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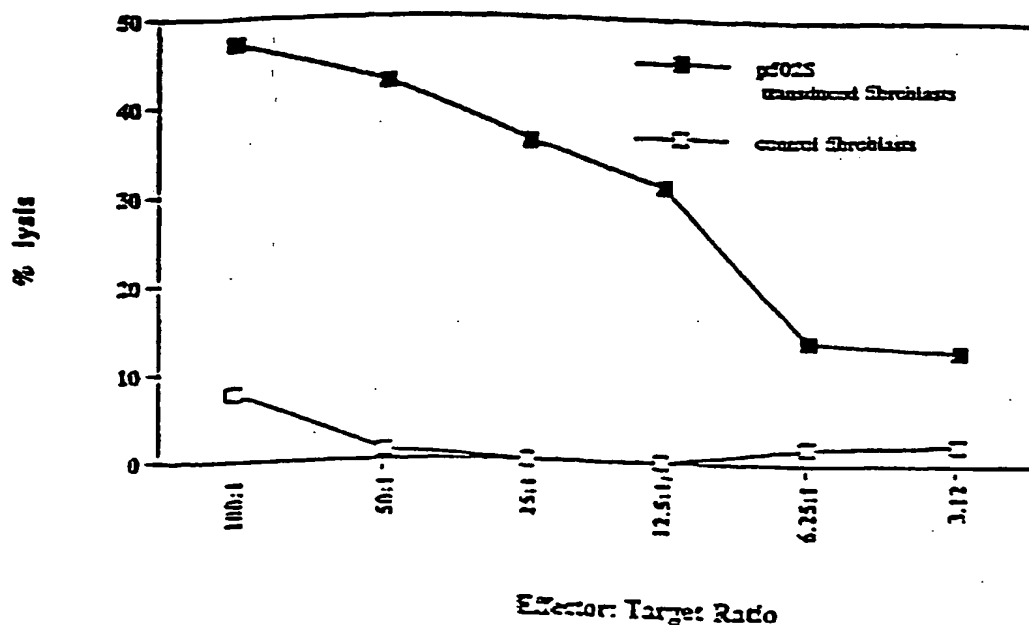
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(54) Title: **COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER**



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.



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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

5 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides
10 are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of prostate cancer.

BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have
15 been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with
20 an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

25 In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA)

and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

10 SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,

381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, under moderately stringent conditions;

5 (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

10 (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

15 (g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

20 In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of prostate tissue samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for other normal tissues.

25 The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences
30 recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383,

477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

In certain preferred embodiments, the polypeptides and/or
5 polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the
10 fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-
15 629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 or 789-791, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626,
20 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

25 Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic
30 applications. Such compositions generally comprise an immunogenic polypeptide or

polynucleotide of the invention and an immunostimulant, such as an adjuvant, together with a physiologically acceptable carrier.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusion proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating and/or enhancing the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for
5 removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the polypeptide from the sample.

Within related aspects, methods are provided for inhibiting the
10 development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a
15 polynucleotide encoding such a polypeptide; and (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for
20 inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide
25 comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a prostate cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide of the present invention, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to an inventive polynucleotide, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample an amount of a polynucleotide that
5 hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as
10 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All
15 references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts.
20 The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of γ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to
25 fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/*neu*.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release

bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8⁺ cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a ⁵¹Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2.

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

5 SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16
SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1
SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4
SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17
SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12
10 SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862
SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13
SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19
15 SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25
SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58
20 SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58
SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63
SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4
25 SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14
SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21
30 SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48

SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55
SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858
5 SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860
SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861
SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864
SEQ ID NO: 41 is the determined cDNA sequence for P5
SEQ ID NO: 42 is the determined cDNA sequence for P8
10 SEQ ID NO: 43 is the determined cDNA sequence for P9
SEQ ID NO: 44 is the determined cDNA sequence for P18
SEQ ID NO: 45 is the determined cDNA sequence for P20
SEQ ID NO: 46 is the determined cDNA sequence for P29
SEQ ID NO: 47 is the determined cDNA sequence for P30
15 SEQ ID NO: 48 is the determined cDNA sequence for P34
SEQ ID NO: 49 is the determined cDNA sequence for P36
SEQ ID NO: 50 is the determined cDNA sequence for P38
SEQ ID NO: 51 is the determined cDNA sequence for P39
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SEQ ID NO: 55 is the determined cDNA sequence for P50
SEQ ID NO: 56 is the determined cDNA sequence for P53
SEQ ID NO: 57 is the determined cDNA sequence for P55
25 SEQ ID NO: 58 is the determined cDNA sequence for P60
SEQ ID NO: 59 is the determined cDNA sequence for P64
SEQ ID NO: 60 is the determined cDNA sequence for P65
SEQ ID NO: 61 is the determined cDNA sequence for P73
SEQ ID NO: 62 is the determined cDNA sequence for P75
30 SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79

SEQ ID NO: 65 is the determined cDNA sequence for P84

SEQ ID NO: 66 is the determined cDNA sequence for P68

SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred

5 to as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82

SEQ ID NO: 69 is the determined cDNA sequence for U1-3064

SEQ ID NO: 70 is the determined cDNA sequence for U1-3065

SEQ ID NO: 71 is the determined cDNA sequence for V1-3692

10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905

SEQ ID NO: 73 is the determined cDNA sequence for V1-3686

SEQ ID NO: 74 is the determined cDNA sequence for R1-2330

SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976

SEQ ID NO: 76 is the determined cDNA sequence for V1-3679

15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736

SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738

SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741

SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744

SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734

20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774

SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781

SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785

SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787

SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796

25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807

SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810

SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811

SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876

SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

30 SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896

- SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761
SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762
SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766
SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770
5 SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771
SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772
SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297
SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309
SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278
10 SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288
SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283
SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304
SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296
SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280
15 SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12
(also referred to as P504S)
SEQ ID NO: 108 is the predicted amino acid sequence for F1-12
SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17
SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12
20 (also referred to as P501S)
SEQ ID NO: 111 is the determined full length cDNA sequence for N1-
1862 (also referred to as P503S)
SEQ ID NO: 112 is the predicted amino acid sequence for J1-17
SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also
25 referred to as P501S)
SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also
referred to as P503S)
SEQ ID NO: 115 is the determined cDNA sequence for P89
SEQ ID NO: 116 is the determined cDNA sequence for P90
30 SEQ ID NO: 117 is the determined cDNA sequence for P92

SEQ ID NO: 118 is the determined cDNA sequence for P95
SEQ ID NO: 119 is the determined cDNA sequence for P98
SEQ ID NO: 120 is the determined cDNA sequence for P102
SEQ ID NO: 121 is the determined cDNA sequence for P110
5 SEQ ID NO: 122 is the determined cDNA sequence for P111
SEQ ID NO: 123 is the determined cDNA sequence for P114
SEQ ID NO: 124 is the determined cDNA sequence for P115
SEQ ID NO: 125 is the determined cDNA sequence for P116
SEQ ID NO: 126 is the determined cDNA sequence for P124
10 SEQ ID NO: 127 is the determined cDNA sequence for P126
SEQ ID NO: 128 is the determined cDNA sequence for P130
SEQ ID NO: 129 is the determined cDNA sequence for P133
SEQ ID NO: 130 is the determined cDNA sequence for P138
SEQ ID NO: 131 is the determined cDNA sequence for P143
15 SEQ ID NO: 132 is the determined cDNA sequence for P151
SEQ ID NO: 133 is the determined cDNA sequence for P156
SEQ ID NO: 134 is the determined cDNA sequence for P157
SEQ ID NO: 135 is the determined cDNA sequence for P166
SEQ ID NO: 136 is the determined cDNA sequence for P176
20 SEQ ID NO: 137 is the determined cDNA sequence for P178
SEQ ID NO: 138 is the determined cDNA sequence for P179
SEQ ID NO: 139 is the determined cDNA sequence for P185
SEQ ID NO: 140 is the determined cDNA sequence for P192
SEQ ID NO: 141 is the determined cDNA sequence for P201
25 SEQ ID NO: 142 is the determined cDNA sequence for P204
SEQ ID NO: 143 is the determined cDNA sequence for P208
SEQ ID NO: 144 is the determined cDNA sequence for P211
SEQ ID NO: 145 is the determined cDNA sequence for P213
SEQ ID NO: 146 is the determined cDNA sequence for P219
30 SEQ ID NO: 147 is the determined cDNA sequence for P237

5 SEQ ID NO: 148 is the determined cDNA sequence for P239
SEQ ID NO: 149 is the determined cDNA sequence for P248
SEQ ID NO: 150 is the determined cDNA sequence for P251
SEQ ID NO: 151 is the determined cDNA sequence for P255
SEQ ID NO: 152 is the determined cDNA sequence for P256
SEQ ID NO: 153 is the determined cDNA sequence for P259
SEQ ID NO: 154 is the determined cDNA sequence for P260
SEQ ID NO: 155 is the determined cDNA sequence for P263
SEQ ID NO: 156 is the determined cDNA sequence for P264
10 SEQ ID NO: 157 is the determined cDNA sequence for P266
SEQ ID NO: 158 is the determined cDNA sequence for P270
SEQ ID NO: 159 is the determined cDNA sequence for P272
SEQ ID NO: 160 is the determined cDNA sequence for P278
SEQ ID NO: 161 is the determined cDNA sequence for P105
15 SEQ ID NO: 162 is the determined cDNA sequence for P107
SEQ ID NO: 163 is the determined cDNA sequence for P137
SEQ ID NO: 164 is the determined cDNA sequence for P194
SEQ ID NO: 165 is the determined cDNA sequence for P195
SEQ ID NO: 166 is the determined cDNA sequence for P196
20 SEQ ID NO: 167 is the determined cDNA sequence for P220
SEQ ID NO: 168 is the determined cDNA sequence for P234
SEQ ID NO: 169 is the determined cDNA sequence for P235
SEQ ID NO: 170 is the determined cDNA sequence for P243
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1
25 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2
SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13
30 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14

SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14

SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-

4736

SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-

5 4738

SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-

4741

SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-

4744

10

SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-

4774

SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-

4781

SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-

15 4785

SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-

4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-

4796

20

SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-

4807

SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810

SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811

SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-

25 4876

SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-

4884

SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-

4896

SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-
4761

SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-
4762

5 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-
4766

SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770
SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771
SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-
10 4772

SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-
4309

SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-
4278

15 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-
4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-
4283

SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-
20 4304

SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-
4296

SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-
4280

25 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd
SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con
SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev
SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd
SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev
30 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd

SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd
5 SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev
SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd
10 SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev
SEQ ID NO: 223 is the determined cDNA sequence for P509S
SEQ ID NO: 224 is the determined cDNA sequence for P510S
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11
15 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23
20 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35
25 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41
30 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42

SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56
5 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84
10 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1
15 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2
SEQ ID NO: 261 is the determined cDNA sequence for JP1D3
20 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6
SEQ ID NO: 265 is the determined cDNA sequence for JP1D6
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5
25 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7
SEQ ID NO: 270 is the determined cDNA sequence for JP1D9
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10
30 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9

5 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12
SEQ ID NO: 275 is the determined cDNA sequence for JP1D11
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11
SEQ ID NO: 277 is the determined cDNA sequence for JP1C12
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12
SEQ ID NO: 280 is the determined cDNA sequence for JP8G2
10 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1
SEQ ID NO: 282 is the determined cDNA sequence for JP8H2
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4
SEQ ID NO: 285 is the determined cDNA sequence for JP8C3
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4
15 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7
20 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7
SEQ ID NO: 293 is the determined cDNA sequence for P8D8
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8
25 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9
30 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9

- SEQ ID NO: 303 is the determined cDNA sequence for JP8C12
SEQ ID NO: 304 is the determined cDNA sequence for JP8E11
SEQ ID NO: 305 is the determined cDNA sequence for JP8E12
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12
5 SEQ ID NO: 307 is the determined cDNA sequence for P711P
SEQ ID NO: 308 is the determined cDNA sequence for P712P
SEQ ID NO: 309 is the determined cDNA sequence for CLONE23
SEQ ID NO: 310 is the determined cDNA sequence for P774P
SEQ ID NO: 311 is the determined cDNA sequence for P775P
10 SEQ ID NO: 312 is the determined cDNA sequence for P715P
SEQ ID NO: 313 is the determined cDNA sequence for P710P
SEQ ID NO: 314 is the determined cDNA sequence for P767P
SEQ ID NO: 315 is the determined cDNA sequence for P768P
SEQ ID NO: 316-325 are the determined cDNA sequences of previously
15 isolated genes
SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5
SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5
SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26
SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26
20 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23
SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23
SEQ ID NO: 332 is the determined full length cDNA sequence for
P509S
SEQ ID NO: 333 is the determined extended cDNA sequence for P707P
25 (also referred to as 11-C9)
SEQ ID NO: 334 is the determined cDNA sequence for P714P
SEQ ID NO: 335 is the determined cDNA sequence for P705P (also
referred to as 9-F3)
SEQ ID NO: 336 is the predicted amino acid sequence for P705P
30 SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

- SEQ ID NO: 338 is the amino acid sequence of the peptide p5
- SEQ ID NO: 339 is the predicted amino acid sequence of P509S
- SEQ ID NO: 340 is the determined cDNA sequence for P778P
- SEQ ID NO: 341 is the determined cDNA sequence for P786P
- 5 SEQ ID NO: 342 is the determined cDNA sequence for P789P
- SEQ ID NO: 343 is the determined cDNA sequence for a clone showing
homology to Homo sapiens MM46 mRNA
- SEQ ID NO: 344 is the determined cDNA sequence for a clone showing
homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA
- 10 SEQ ID NO: 345 is the determined cDNA sequence for a clone showing
homology to Homo sapiens mRNA for E-cadherin
- SEQ ID NO: 346 is the determined cDNA sequence for a clone showing
homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase
(SHMT)
- 15 SEQ ID NO: 347 is the determined cDNA sequence for a clone showing
homology to Homo sapiens natural resistance-associated macrophage protein2
(NRAMP2)
- SEQ ID NO: 348 is the determined cDNA sequence for a clone showing
homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)
- 20 SEQ ID NO: 349 is the determined cDNA sequence for a clone showing
homology to Human mRNA for proteosome subunit p40
- SEQ ID NO: 350 is the determined cDNA sequence for P777P
- SEQ ID NO: 351 is the determined cDNA sequence for P779P
- SEQ ID NO: 352 is the determined cDNA sequence for P790P
- 25 SEQ ID NO: 353 is the determined cDNA sequence for P784P
- SEQ ID NO: 354 is the determined cDNA sequence for P776P
- SEQ ID NO: 355 is the determined cDNA sequence for P780P
- SEQ ID NO: 356 is the determined cDNA sequence for P544S
- SEQ ID NO: 357 is the determined cDNA sequence for P745S
- 30 SEQ ID NO: 358 is the determined cDNA sequence for P782P

- SEQ ID NO: 359 is the determined cDNA sequence for P783P
SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984
SEQ ID NO: 361 is the determined cDNA sequence for P787P.
SEQ ID NO: 362 is the determined cDNA sequence for P788P
5 SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994
SEQ ID NO: 364 is the determined cDNA sequence for P781P
SEQ ID NO: 365 is the determined cDNA sequence for P785P
SEQ ID NO: 366-375 are the determined cDNA sequences for splice
variants of B305D.
- 10 SEQ ID NO: 376 is the predicted amino acid sequence encoded by the
sequence of SEQ ID NO: 366.
SEQ ID NO: 377 is the predicted amino acid sequence encoded by the
sequence of SEQ ID NO: 372.
SEQ ID NO: 378 is the predicted amino acid sequence encoded by the
15 sequence of SEQ ID NO: 373.
SEQ ID NO: 379 is the predicted amino acid sequence encoded by the
sequence of SEQ ID NO: 374.
SEQ ID NO: 380 is the predicted amino acid sequence encoded by the
sequence of SEQ ID NO: 375.
- 20 SEQ ID NO: 381 is the determined cDNA sequence for B716P.
SEQ ID NO: 382 is the determined full-length cDNA sequence for
P711P.
SEQ ID NO: 383 is the predicted amino acid sequence for P711P.
SEQ ID NO: 384 is the cDNA sequence for P1000C.
25 SEQ ID NO: 385 is the cDNA sequence for CGI-82.
SEQ ID NO: 386 is the cDNA sequence for 23320.
SEQ ID NO: 387 is the cDNA sequence for CGI-69.
SEQ ID NO: 388 is the cDNA sequence for L-iditol-2-dehydrogenase.
SEQ ID NO: 389 is the cDNA sequence for 23379.
30 SEQ ID NO: 390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

5 SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor

PDEF.

10 SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

15 SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553 (also known as

P1020C).

20 SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

25 SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571.

SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

30 SEQ ID NO:418 is the cDNA sequence for 22575.

SEQ ID NO:419 is the cDNA sequence for 22580.
SEQ ID NO:420 is the cDNA sequence for 22581.
SEQ ID NO:421 is the cDNA sequence for 22582.
SEQ ID NO:422 is the cDNA sequence for 22583.
5 SEQ ID NO:423 is the cDNA sequence for 22584.
SEQ ID NO:424 is the cDNA sequence for 22585.
SEQ ID NO:425 is the cDNA sequence for 22586.
SEQ ID NO:426 is the cDNA sequence for 22587.
SEQ ID NO:427 is the cDNA sequence for 22588.
10 SEQ ID NO:428 is the cDNA sequence for 22589.
SEQ ID NO:429 is the cDNA sequence for 22590.
SEQ ID NO:430 is the cDNA sequence for 22591.
SEQ ID NO:431 is the cDNA sequence for 22592.
SEQ ID NO:432 is the cDNA sequence for 22593.
15 SEQ ID NO:433 is the cDNA sequence for 22594.
SEQ ID NO:434 is the cDNA sequence for 22595.
SEQ ID NO:435 is the cDNA sequence for 22596.
SEQ ID NO:436 is the cDNA sequence for 22847.
SEQ ID NO:437 is the cDNA sequence for 22848.
20 SEQ ID NO:438 is the cDNA sequence for 22849.
SEQ ID NO:439 is the cDNA sequence for 22851.
SEQ ID NO:440 is the cDNA sequence for 22852.
SEQ ID NO:441 is the cDNA sequence for 22853.
SEQ ID NO:442 is the cDNA sequence for 22854.
25 SEQ ID NO:443 is the cDNA sequence for 22855.
SEQ ID NO:444 is the cDNA sequence for 22856.
SEQ ID NO:445 is the cDNA sequence for 22857.
SEQ ID NO:446 is the cDNA sequence for 23601.
SEQ ID NO:447 is the cDNA sequence for 23602.
30 SEQ ID NO:448 is the cDNA sequence for 23605.

- SEQ ID NO:449 is the cDNA sequence for 23606.
SEQ ID NO:450 is the cDNA sequence for 23612.
SEQ ID NO:451 is the cDNA sequence for 23614.
SEQ ID NO:452 is the cDNA sequence for 23618.
5 SEQ ID NO:453 is the cDNA sequence for 23622.
SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
SEQ ID NO:455 is the cDNA sequence for LIM protein.
SEQ ID NO:456 is the cDNA sequence for a known gene.
SEQ ID NO:457 is the cDNA sequence for a known gene.
10 SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
SEQ ID NO:459 is the cDNA sequence for 23045.
SEQ ID NO:460 is the cDNA sequence for 23032.
SEQ ID NO:461 is the cDNA sequence for clone 23054.
SEQ ID NO:462-467 are cDNA sequences for known genes.
15 SEQ ID NO:468-471 are cDNA sequences for P710P.
SEQ ID NO:472 is a cDNA sequence for P1001C.
SEQ ID NO: 473 is the determined cDNA sequence for a first splice
variant of P775P (referred to as 27505).
SEQ ID NO: 474 is the determined cDNA sequence for a second splice
20 variant of P775P (referred to as 19947).
SEQ ID NO: 475 is the determined cDNA sequence for a third splice
variant of P775P (referred to as 19941).
SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice
variant of P775P (referred to as 19937).
25 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the
sequence of SEQ ID NO: 474.
SEQ ID NO: 478 is a second predicted amino acid sequence encoded by
the sequence of SEQ ID NO: 474.
SEQ ID NO: 479 is the predicted amino acid sequence encoded by the
30 sequence of SEQ ID NO: 475.

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

5 SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

10 SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

15 SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

20 SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

25 SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

30 SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ
ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

5 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID
NO: 366.

10 SEQ ID NO: 531 is the cDNA sequence of the open reading frame of
SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of
SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

15 SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ
ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ
ID NO: 535.

20 SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ
ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

SEQ ID NO: 540 is the peptide P501S-376.

25 SEQ ID NO: 541-551 are epitopes of P501S.

SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by
predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

30 SEQ ID NO: 570 is the determined cDNA sequence for a splice variant
of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

5 SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

10 SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

15 SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

20 SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.

SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

25 SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

30 SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

5 SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P
and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and
PSA.

SEQ ID NO: 618 is the cDNA sequence of the gene DD3.

10 SEQ ID NO: 619 is an extended cDNA sequence for P714P.

SEQ ID NO: 620-622 are the cDNA sequences for splice variants of
P704P.

SEQ ID NO: 623 is the cDNA sequence of a splice variant of P553S
referred to as P553S-14.

15 SEQ ID NO: 624 is the cDNA sequence of a splice variant of P553S
referred to as P553S-12.

SEQ ID NO: 625 is the cDNA sequence of a splice variant of P553S
referred to as P553S-10.

20 SEQ ID NO: 626 is the cDNA sequence of a splice variant of P553S
referred to as P553S-6.

SEQ ID NO: 627 is the amino acid sequence encoded by SEQ ID NO:
626.

SEQ ID NO: 628 is a first amino acid sequence encoded by SEQ ID NO:
623.

25 SEQ ID NO: 629 is a second amino acid sequence encoded by SEQ ID
NO: 623.

SEQ ID NO: 630 is a first full-length cDNA sequence for prostate-
specific transglutaminase gene (also referred to herein as P558S).

30 SEQ ID NO: 631 is a second full-length cDNA sequence for prostate-
specific transglutaminase gene.

SEQ ID NO: 632 is the amino acid sequence encoded by the sequence of SEQ ID NO: 630.

SEQ ID NO: 633 is the amino acid sequence encoded by the sequence of SEQ ID NO: 631.

5 SEQ ID NO: 634 is the full-length cDNA sequence for P788P.

SEQ ID NO: 635 is the amino acid sequence encoded by SEQ ID NO: 634.

SEQ ID NO: 636 is the determined cDNA sequence for a polymorphic variant of P788P.

10 SEQ ID NO: 637 is the amino acid sequence encoded by SEQ ID NO: 636.

SEQ ID NO: 638 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 639 is the cDNA sequence that encodes peptide 4 from P703P.

15 SEQ ID NO: 640-655 are cDNA sequences encoding epitopes of P703P.

SEQ ID NO: 656-671 are the amino acid sequences of epitopes of P703P.

SEQ ID NO: 672 and 673 are PCR primers.

20 SEQ ID NO: 674 is the cDNA sequence encoding an N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 675 is the amino acid sequence of the N-terminal portion of P788P expressed in *E. coli*.

SEQ ID NO: 676 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

25 SEQ ID NO: 677 and 678 are PCR primers.

SEQ ID NO: 679 is the cDNA sequence for the Ra12-P510S-C construct.

SEQ ID NO: 680 is the cDNA sequence for the P510S-C construct.

SEQ ID NO: 681 is the cDNA sequence for the P510S-E3 construct.

SEQ ID NO: 682 is the amino acid sequence for the Ra12-P510S-C construct.

SEQ ID NO: 683 is the amino acid sequence for the P510S-C construct.

SEQ ID NO: 684 is the amino acid sequence for the P510S-E3 construct.

5 SEQ ID NO: 685-690 are PCR primers.

SEQ ID NO: 691 is the cDNA sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 692 is the amino acid sequence of the construct Ra12-P775P-ORF3.

10 SEQ ID NO: 693 and 694 are PCR primers.

SEQ ID NO: 695 is the determined amino acid sequence for a P703P His tag fusion protein.

SEQ ID NO: 696 is the determined cDNA sequence for a P703P His tag fusion protein.

15 SEQ ID NO: 697 and 698 are PCR primers.

SEQ ID NO: 699 is the determined amino acid sequence for a P705P His tag fusion protein.

SEQ ID NO: 700 is the determined cDNA sequence for a P705P His tag fusion protein.

20 SEQ ID NO: 701 and 702 are PCR primers.

SEQ ID NO: 703 is the determined amino acid sequence for a P711P His tag fusion protein.

SEQ ID NO: 704 is the determined cDNA sequence for a P711P His tag fusion protein.

25 SEQ ID NO: 705 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 706 and 707 are PCR primers.

SEQ ID NO: 708 is the determined cDNA sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 709 is the determined amino acid sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 710 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 711 is the DNA sequence encoding SEQ ID NO: 710.

5 SEQ ID NO: 712 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 713 is the DNA sequence encoding SEQ ID NO: 712.

SEQ ID NO: 714 is a peptide employed in epitope mapping studies.

SEQ ID NO: 715 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 716 is the DNA sequence encoding SEQ ID NO: 715.

10 SEQ ID NO: 717-719 are the amino acid sequences for CD4 epitopes of P501S.

SEQ ID NO: 720-722 are the DNA sequences encoding the sequences of SEQ ID NO: 717-719.

15 SEQ ID NO: 723-734 are the amino acid sequences for putative CTL epitopes of P703P.

SEQ ID NO: 735 is the full-length cDNA sequence for P789P.

SEQ ID NO: 736 is the amino acid sequence encoded by SEQ ID NO: 735.

20 SEQ ID NO: 737 is the determined full-length cDNA sequence for the splice variant of P776P referred to as contig 6.

SEQ ID NO: 738-739 are determined full-length cDNA sequences for the splice variant of P776P referred to as contig 7.

SEQ ID NO: 740-744 are amino acid sequences encoded by SEQ ID NO: 737.

25 SEQ ID NO: 745-750 are amino acid sequences encoded by the splice variant of P776P referred to as contig 7.

SEQ ID NO: 751 is the full-length cDNA sequence for human transmembrane protease serine 2.

30 SEQ ID NO: 752 is the amino acid sequence encoded by SEQ ID NO: 751.

SEQ ID NO: 753 is the cDNA sequence encoding the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 754 is the first 209 amino acids of human transmembrane protease serine 2,

5 SEQ ID NO: 755 is the amino acid sequence of peptide 296-322 of P501S.

SEQ ID NO: 756-759 are PCR primers.

SEQ ID NO: 760 is the determined cDNA sequence of the Vb chain of a T cell receptor for the P501S-specific T cell clone 4E5.

10 SEQ ID NO: 761 is the determined cDNA sequence of the Va chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 762 is the amino acid sequence encoded by SEQ ID NO 760.

15 SEQ ID NO: 763 is the amino acid sequence encoded by SEQ ID NO 761.

SEQ ID NO: 764 is the full-length open reading frame for P768P including stop codon.

SEQ ID NO: 765 is the full-length open reading frame for P768P without stop codon.

20 SEQ ID NO: 766 is the amino acid sequence encoded by SEQ ID NO: 765.

SEQ ID NO: 767-772 are the amino acid sequences for predicted domains of P768P.

SEQ ID NO: 773 is the full-length cDNA sequence of P835P.

25 SEQ ID NO: 774 is the cDNA sequence of the previously identified clone FLJ13581.

SEQ ID NO: 775 is the cDNA sequence of the open reading frame for P835P with stop codon.

30 SEQ ID NO: 776 is the cDNA sequence of the open reading frame for P835P without stop codon.

SEQ ID NO: 777 is the full-length amino acid sequence for P835P.

SEQ ID NO: 778-785 are the amino acid sequences of extracellular and intracellular domains of P835P.

SEQ ID NO: 786 is the full-length cDNA sequence for P1000C.

5 SEQ ID NO: 787 is the cDNA sequence of the open reading frame for P1000C, including stop codon.

SEQ ID NO: 788 is the cDNA sequence of the open reading frame for P1000C, without stop codon.

SEQ ID NO: 789 is the full-length amino acid sequence for P1000C.

10 SEQ ID NO: 790 is amino acids 1-100 of SEQ ID NO: 789.

SEQ ID NO: 791 is amino acids 100-492 of SEQ ID NO: 789.

SEQ ID NO: 792 is the amino acid sequence of an α prepro-P501S recombinant protein.

15 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly prostate cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such
20 polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (e.g., T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of
25 the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, e.g., Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

5 All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

Polypeptide Compositions

10 As used herein, the term "polypeptide" is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-
15 expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic
20 determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382
25 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175,

177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In specific embodiments, the polypeptides of the invention
5 comprise amino acid sequences as set forth in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

10 The polypeptides of the present invention are sometimes herein referred to as prostate-specific proteins or prostate-specific polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in prostate tissue samples. Thus, a "prostate-specific polypeptide" or "prostate-specific protein," refers generally to a polypeptide sequence of the present
15 invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of prostate tissue samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of prostate tissue samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other
20 normal tissues, as determined using a representative assay provided herein. A prostate-specific polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are
25 immunogenic, i.e., they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with prostate cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory
30 Manual*, Cold Spring Harbor Laboratory, 1988. In one illustrative example, a

polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

5 As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide.

10 Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they

15 specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that

20 is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that

25 have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain

30 has been deleted. Other illustrative immunogenic portions will contain a small N-

and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide composition set forth herein, such as those set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95 %, 96%, 97%, 98%, or 99% or more identity

(determined as described below), along its length, to a polypeptide sequence set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, e.g., with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or

even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

In making such changes, the hydrophatic index of amino acids may be considered. The importance of the hydrophatic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydrophatic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydrophatic index on the basis of its

hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5);
5 glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are
10 within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of
15 its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine
20 (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2
25 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that
30 take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of
5 flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values
15 include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a
20 preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

25 As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For
30 example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known

tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al.,

Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to
5 separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and
10 transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus,
15 tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression
20 and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent
25 and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; *see also*, Skeiky et al., *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the
30 purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous

immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine

amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been
5 exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at
10 residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention,
15 when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4⁺ T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further
20 described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a
25 growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of
30 the invention are isolated. An "isolated" polypeptide is one that is removed from its

original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably an immunogenic variant or derivative, of such a sequence.

5 Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655,
10 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722,
15 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765,
20 773-776 and 786-788. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-
25 335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a
30 polynucleotide sequence of this invention using the methods described herein, (*e.g.*,

BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to, or complementary to, one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for

20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable
5 highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides
10 that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

15 The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment
20 of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated
25 to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison
30 window to identify and compare local regions of sequence similarity. A "comparison

window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- 5 Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.
- 10 In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson,
- 15 E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be

20 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

25 Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402

30 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST

2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides

that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 contiguous nucleotides that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of

complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of
5 contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in
10 various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger
15 contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in
20 length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

25 Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various

factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to

destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary,

and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m , binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a

high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement
5 that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general,
10 enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to
15 cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many
20 technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of
25 target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action
30 (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the

specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO

92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes

expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number of methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, *Science*. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, *Bioorg Med Chem.* 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*,

Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

Polynucleotide Identification, Characterization and Expression

Polynucleotide compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCRTM, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCRTM amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCRTM amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (see Triglia et al., *Nucl. Acids Res.* 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of

amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al.; *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al.; *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be

confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5 In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, i.e., a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing
10 sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et
15 al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,
20 or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

25 The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription
30 and translation elements, including constitutive and inducible promoters, may be used.

For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSFORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For

example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or apt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

5 A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal
10 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

15 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions
20 thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used
25 include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

 Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained
30 intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as

"framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation

of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')₂" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V_H::V_L heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an

antigen-binding site. See, e.g., U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (e.g., a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) *Nature* 349:293-299; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220-4224; Shaw et al. (1987) *J Immunol.* 138:4534-4538; and Brown et al. (1987) *Cancer Res.* 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) *Nature* 332:323-327; Verhoeyen et al. (1988) *Science* 239:1534-1536; and Jones et al. (1986) *Nature* 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, e.g., a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) *Ann. Rev. Biochem.* 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (e.g., solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (e.g., electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in

this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the

intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by
5 serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.
10 Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent
15 bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for
20 radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For
25 example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells

may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et

al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as

described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve

the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et al. (1994) *J. Virol.* 68:933-940; Barr et al. (1994) *Gene Therapy* 1:51-58; Berkner, K. L. (1988) *BioTechniques* 6:616-629; and Rich et al. (1993) *Human Gene Therapy* 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) *Molec. Cell. Biol.* 8:3988-3996; Vincent et al. (1990) *Vaccines 90* (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) *Current Opinion in Biotechnology* 3:533-539; Muzyczka, N. (1992) *Current Topics in Microbiol. and Immunol.* 158:97-129;

Kotin, R. M. (1994) *Human Gene Therapy* 5:793-801; Shelling and Smith (1994) *Gene Therapy* 1:165-169; and Zhou et al. (1994) *J. Exp. Med.* 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK^{sup}(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, e.g., Elroy-Stein and Moss, *Proc. Natl. Acad. Sci. USA* (1990) 87:6743-6747; Fuerst et al. *Proc. Natl. Acad. Sci. USA* (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer

protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, e.g., WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in a specific location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of

DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression
5 construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable
10 beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK)
15 and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device,
20 propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639
25 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances
30 or potentiates an immune response (antibody and/or cell-mediated) to an exogenous

antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins.

5 Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated

10 sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition

15 is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as

20 provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman,

25 *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL[®] adjuvants are available from Corixa Corporation (Seattle, WA; see, for example, US

30 Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing

oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by
5 Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example
10 combinations of at least two of the following group comprising QS21, QS7, Quil A, β -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix,
15 particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or
20 suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol^R to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the
25 combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL[®] adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-

MPL[®] adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn[®]; Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula



wherein, n is 1-50, A is a bond or $-\text{C}(\text{O})-$, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein n is between 1 and 50, preferably 4-24, most preferably 9; the R component is C_{1-50} , preferably $\text{C}_4\text{-C}_{20}$ alkyl and most preferably C_{12} alkyl, and A is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Poxyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12th edition: entry 7717). These adjuvant molecules are described in WO

99/52549. The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

5 According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or
10 maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

15 Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In
20 general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex*
25 *vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

 Dendritic cells and progenitors may be obtained from peripheral blood,
30 bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph

nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF α to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc γ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated
5 immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration,
10 including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release.
15 In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers
20 include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends
25 upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S.
30 Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763;

5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including e.g., oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they

may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration, the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or

by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

- 5 Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered
10 isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml
15 of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity
20 standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for
25 example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be

administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption
5 delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase
10 "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the
15 lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of
20 a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid
25 particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example,
30 Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

5 Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery
10 systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

15 In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

 Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the
20 present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for
25 example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of prostate cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see, for example, Cheever et al., Immunological Reviews 157:177, 1997*).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g., intracutaneous,*

intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μ g to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies)

obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the
5 biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in
10 the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c)
15 comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding
20 agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized
25 binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and polypeptide portions thereof to which the binding agent binds, as
30 described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989*).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the

cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound
5 binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific
10 for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

15 The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein.
20 Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

25 Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be

present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

5

EXAMPLES

EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

10

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A⁺ RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following
15 the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen,
20 Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of
25 pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the
30 percentage of clones that carried insert, the average insert size and by sequence analysis.

The prostate tumor library contained 1.64×10^7 independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained 3.3×10^6 independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 μ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μ l of H₂O, heat-denatured and mixed with 100 μ l (100 μ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μ l H₂O to form the driver DNA.

To form the tracer DNA, 10 μ g prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μ l H₂O. Tracer DNA was mixed with 15 μ l driver DNA and 20 μ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μ l H₂O, mixed with 8 μ l driver DNA and 20 μ l of 2 x hybridization buffer, and subjected to a hybridization at 68

^{60}C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK⁺ (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted
5 cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems
10 Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided
15 in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA),
20 human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence
25 for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described
30 above with the normal pancreas cDNA library and with the three most abundant genes

in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 μ g each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

- 5 In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively.
- 10 Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

- A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences
- 15 with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

- Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and
- 25 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the
- 30

isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the

determination of extended cDNA sequences for 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

EXAMPLE 2

DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2 μ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using β -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the β -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin,

small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be

over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. Subsequent comparison of the sequence of SEQ ID NO: 384 with sequences in the public databases, led to the identification of a full-length cDNA sequence of P1000C (SEQ ID NO: 786), which encodes a 492 amino acid sequence.

Analysis of the amino acid sequence using the PSORT II program led to the

identification of a putative transmembrane domain from amino acids 84-100. The cDNA sequence of the open reading frame of P1000C, including the stop codon, is provided in SEQ ID NO: 787, with the open reading frame without the stop codon being provided in SEQ ID NO: 788. The full-length amino acid sequence of P1000C is provided in SEQ ID NO: 789. SEQ ID NO: 790 and 791 represent amino acids 1-100 and 100-492 of P1000C, respectively.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC
POLYPEPTIDES BY PCR-BASED SUBTRACTION

5 A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The
10 resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

 Fifty-nine positive clones were sequenced. Comparison of the DNA
15 sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID
20 NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

 Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences
25 which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 620-622.

 Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA
30 sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145,

147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones
5 containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is
10 provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine
15 and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed
20 comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor
25 compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal
30 prostate and prostate tumor, compared to six of twelve other normal tissues tested.

Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and
5 normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-
10 h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in
15 the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

20 mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor
25 and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

Using computer algorithms, the following regions of P703P were predicted to represent potential HLA A2-binding CTL epitopes: amino acids 164-172 of SEQ ID NO: 525 (SEQ ID NO: 723); amino acids 160-168 of SEQ ID NO: 525 (SEQ ID NO: 724); amino acids 239-247 of SEQ ID NO: 525 (SEQ ID NO: 725); amino acids 118-126 of SEQ ID NO: 525 (SEQ ID NO: 726); amino acids 112-120 of SEQ ID NO: 525 (SEQ ID NO: 727); amino acids 155-164 of SEQ ID NO: 525 (SEQ ID NO: 728); amino acids 117-126 of SEQ ID NO: 525 (SEQ ID NO: 729); amino acids 164-173 of SEQ ID NO: 525 (SEQ ID NO: 730); amino acids 154-163 of SEQ ID NO:

525 (SEQ ID NO: 731); amino acids 163-172 of SEQ ID NO: 525 (SEQ ID NO: 732); amino acids 58-66 of SEQ ID NO: 525 (SEQ ID NO: 733); and amino acids 59-67 of SEQ ID NO: 525 (SEQ ID NO: 734).

P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorigenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

To determine whether P703P expression increases with increased severity of Gleason grade, an indicator of tumor stage, quantitative PCR analysis was performed on prostate tumor samples with a range of Gleason scores from 5 to > 8. The mean level of P703P expression increased with increasing Gleason score, indicating that P703P expression may correlate with increased disease severity.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are

provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P

were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence is provided in SEQ ID NO: 619. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

5 Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

10 Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an
15 ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on
20 chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential
25 open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The
30 full-length sequences for the two forms are provided in SEQ ID NO: 630 and 631, with

the corresponding amino acid sequences being provided in SEQ ID NO: 632 and 633, respectively. The cDNA sequence of SEQ ID NO: 631 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 633). This insert is not present in the sequence of SEQ ID NO: 630.

5 Further studies on P768P (SEQ ID NO: 315) led to the identification of the putative full-length open reading frame (ORF). The cDNA sequence of the ORF with stop codon is provided in SEQ ID NO: 764. The cDNA sequence of the ORF without stop codon is provided in SEQ ID NO: 765, with the corresponding amino acid sequence being provided in SEQ ID NO: 766. This sequence was found to show 86%
10 identity to a rat calcium transporter protein, indicating that P768P may represent a human calcium transporter protein. The locations of transmembrane domains within P768P were predicted using the PSORT II computer algorithm. Six transmembrane domains were predicted at amino acid positions 118-134, 172-188, 211-227, 230-246, 282-298 and 348-364. The amino acid sequences of SEQ ID NO: 767-772 represent
15 amino acids 1-134, 135-188, 189-227, 228-246, 247-298 and 299-511 of P768P, respectively.

EXAMPLE 4

SYNTHESIS OF POLYPEPTIDES

20

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of
25 conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid
30 (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of

0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

5

EXAMPLE 5

FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

10 A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide
15 restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

20 The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate
25 hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences
30 which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich
5 differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

10 In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for
15 proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA
20 sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant
25 homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most
30 prostate tumors and BPH tissues by a factor of three or greater, with elevated expression

seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

5 Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349,
10 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant
15 homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is
20 provided in SEQ ID NO: 634, with the corresponding predicted amino acid being provided in SEQ ID NO: 635. Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 634, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of
25 P788P is provided in SEQ ID NO: 636, with the corresponding amino acid sequence being provided in SEQ ID NO: 637. The sequence of SEQ ID NO: 637 differs from that of SEQ ID NO: 635 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively. Further studies led to the isolation of the full-length sequence for the clone of SEQ ID NO: 570 (provided in SEQ ID NO: 737). Full-length cloning efforts on the clone of SEQ ID NO: 571 led to the isolation of two sequences (provided in SEQ ID NO: 738 and 739), representing a single clone, that are identical with the exception of a polymorphic insertion/deletion at position 1293. Specifically, the clone of SEQ ID NO: 739 (referred to as clone F1) has a C at position 1293. The clone of SEQ ID NO: 738 (referred to as clone F2) has a single base pair deletion at position 1293. The predicted amino acid sequences encoded by 5 open reading frames located within SEQ ID NO: 737 are provided in SEQ ID NO: 740-744, with the predicted amino acid sequences encoded by the clone of SEQ ID NO: 738 and 739 being provided in SEQ ID NO: 745-750.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common,

suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

5 The clone of SEQ ID NO: 342 (referred to as P789P) was found to show homology to a previously identified gene. The full length cDNA sequence for P789P and the corresponding amino acid sequence are provided in SEQ ID NO: 735 and 736, respectively.

10 EXAMPLE 6

PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

15 Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were
20 immunized with 100µg of P2S#12 and 120µg of an I-A^b binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6×10^6 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium
25 pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2×10^{-5} M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells (5×10^5 /ml) were
30 restimulated with 2.5×10^6 /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells

(Sherman et al, *Science* 258:815-818, 1992) and 3×10^6 /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1×10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 μ g/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes,

CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

5 Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg of an I-A^b binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single
10 cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6×10^6 cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2µg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later cells (5×10^5 /ml) were restimulated
15 with 2.5×10^6 /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3×10^6 /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as
20 shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1×10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were
25 isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION
WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred
5 to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research
Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012
either intramuscularly or intradermally. The mice were immunized three times, with a
two week interval between immunizations. Two weeks after the last immunization,
immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator
10 cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL
activity was assessed against P501S transduced targets. Two out of 8 mice developed
strong anti-P501S CTL responses. These results demonstrate that P501S contains at
least one naturally processed HLA-A2-restricted CTL epitope.

15

EXAMPLE 8

ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate
tumor polypeptide to recognize human tumor.

20

Human CD8⁺ T cells were primed *in vitro* to the P2S-12 peptide (SEQ
ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells
according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75,
1998). The resulting CD8⁺ T cell microcultures were tested for their ability to
recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which
25 were transduced to express the P502S gene in a γ -interferon ELISPOT assay (see
Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). Briefly, titrating numbers of T cells
were assayed in duplicate on 10⁴ fibroblasts in the presence of 3 µg/ml human β_2 -
microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells
were simultaneously assayed on autologous fibroblasts transduced with the P502S gene
30 or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the

fibroblasts were treated with 10 ng/ml γ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a γ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of γ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of γ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

EXAMPLE 9

ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8⁺ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts

retrovirally transduced to express P501S and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays (^{51}Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see* above and Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

10

EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN THE
PROSTATE-SPECIFIC ANTIGEN P703P

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100 μg of p5 peptide together with 140 μg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the

30

control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 638, with the corresponding cDNA sequence being provided in SEQ ID NO: 639.

Twenty 15-mer peptides overlapping by 10 amino acids and derived from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration of 0.25 microgram/ml. Pulsed DC were washed and plated at 1×10^4 cells/well of 96-well V-bottom plates and purified CD4 T cells were added at 1×10^5 /well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2. Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation and cytokine production in response to the

stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by ³H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 638). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVS VVS (SEQ ID NO: 638) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of

recombinant P703P sources were utilized; *E. coli*-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were *E. coli*-derived L3E (a lung-specific antigen) and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both *E. coli* forms of P703P as well as Pichia-derived recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the *E. coli* and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 656-671, with the corresponding cDNA sequences being provided in SEQ ID NO: 640-655, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cell lines were restimulated on the

appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested; line I-1A
5 recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either
10 peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 671; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 668; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 667; corresponding to a.a. 135-149 of
15 SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

EXAMPLE 11

EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

20 Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences
25 for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a
30 frameshift in the open reading frame. The determined DNA sequence of this ORF is

provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

EXAMPLE 12

15 GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH THE PROSTATE-SPECIFIC ANTIGEN P501S

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- γ ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 μ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated

using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8⁺ T cell lines were identified that specifically produced interferon- γ when stimulated with P501S and CD80-transduced autologous
5 fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon- γ in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8⁺ CTL response to P501S can be elicited.

10 To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT
15 assays against these A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid
20 residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-gamma assay. Only peptides P501S-369(20)
25 and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

A naturally processed, CD8, class I-restricted peptide epitope of P501S was identified as follows. Dendritic Cells (DC) were isolated by Percol gradient followed by differential adherence, and cultured for 5 days in the presence of RPMI medium containing 1% human serum, 50ng/ml GM-CSF and 30ng/ml IL-4. Following culture, DC were infected for 24 hours with P501S-expressing adenovirus at an MOI of 10 and matured for an additional 24 hours by the addition of 2ug/ml CD40 ligand. CD8 cells were enriched for by the subtraction of CD4+, CD14+ and CD16+ populations from PBMC with magnetic beads. Priming cultures containing 10,000 P501S-expressing DC and 100,000 CD8+ T cells per well were set up in 96-well V-bottom plates with RPMI containing 10% human serum, 5ng/ml IL-12 and 10ng/ml IL-6. Cultures were stimulated every 7 days using autologous fibroblasts retrovirally

transduced to express P501S and CD80, and were treated with IFN-gamma for 48-72 hours to upregulate MHC Class I expression. 10u/ml IL-2 was added at the time of stimulation and on days 2 and 5 following stimulation. Following 4 stimulation cycles, one P501S-specific CD8+ T cell line (referred to as 2A2) was identified that produced IFN-gamma in response to IFN-gamma-treated P501S/CD80 expressing autologous fibroblasts, but not in response to IFN-gamma-treated P703P/CD80 expressing autologous fibroblasts in a γ -IFN Elispot assay. Line 2A2 was cloned in 96-well plates with 0.5 cell/well or 2 cells/well in the presence of 75,000 PBMC/well, 10,000 B-LCL/well, 30ng/ml OKT3 and 50u/ml IL-2. Twelve clones were isolated that showed strong P501S specificity in response to transduced fibroblasts.

Fluorescence activated cell sorting (FACS) analysis was performed on P501S-specific clones using CD3-, CD4- and CD8-specific antibodies conjugated to PercP, FITC and PE respectively. Consistent with the use of CD8 enriched T cells in the priming cultures, P5401S-specific clones were determined to be CD3+, CD8+ and CD4-.

To identify the relevant P501S epitope recognized by P501S specific CTL, pools of 18-20 mer or 30-mer peptides that spanned the majority of the amino acid sequence of P501S were loaded onto autologous B-LCL and tested in γ -IFN Elispot assays for the ability to stimulate two P501S-specific CTL clones, referred to as 4E5 and 4E7. One pool, composed of five 18-20 mer peptides that spanned amino acids 411-486 of P501S (SEQ ID NO: 113), was found to be recognized by both P501S-specific clones. To identify the specific 18-20 mer peptide recognized by the clones, each of the 18-20 mer peptides that comprised the positive pool were tested individually in γ -IFN Elispot assays for the ability to stimulate the two P501S-specific CTL clones, 4E5 and 4E7. Both 4E5 and 4E7 specifically recognized one 20-mer peptide (SEQ ID NO: 710; cDNA sequence provided in SEQ ID NO: 711) that spanned amino acids 453-472 of P501S. Since the minimal epitope recognized by CD8+ T cells is almost always either a 9 or 10-mer peptide sequence, 10-mer peptides that spanned the entire sequence of SEQ ID NO: 710 were synthesized that differed by 1 amino acid. Each of these 10-mer peptides was tested for the ability to stimulate two P501S-specific clones, (referred to as 1D5 and 1E12). One 10-mer peptide (SEQ ID NO: 712; cDNA sequence provided in

SEQ ID NO: 713) was identified that specifically stimulated the P501S-specific clones. This epitope spans amino acids 463-472 of P501S. This sequence defines a minimal 10-mer epitope from P501S that can be naturally processed and to which CTL responses can be identified in normal PBMC. Thus, this epitope is a candidate for use as a vaccine moiety, and as a therapeutic and/or diagnostic reagent for prostate cancer.

To identify the class I restriction element for the P501S-derived sequence of SEQ ID NO: 712, HLA blocking and mismatch analyses were performed. In γ -IFN Elispot assays, the specific response of clones 4A7 and 4E5 to P501S-transduced autologous fibroblasts was blocked by pre-incubation with 25ug/ml W6/32 (pan-Class I blocking antibody) and B1.23.2 (HLA-B/C blocking antibody). These results demonstrate that the SEQ ID NO: 712-specific response is restricted to an HLA-B or HLA-C allele.

For the HLA mismatch analysis, autologous B-LCL (HLA-A1,A2,B8,B51, Cw1, Cw7) and heterologous B-LCL (HLA-A2,A3,B18,B51,Cw5,Cw14) that share the HLAB51 allele were pulsed for one hour with 20ug/ml of peptide of SEQ ID NO: 712, washed, and tested in γ -IFN Elispot assays for the ability to stimulate clones 4A7 and 4E5. Antibody blocking assays with the B1.23.2 (HLA-B/C blocking antibody) were also performed. SEQ ID NO: 712-specific response was detected using both the autologous (D326) and heterologous (D107) B-LCL, and furthermore the responses were blocked by pre-incubation with 25ug/ml of B1.23.2 HLA-B/C blocking antibody. Together these results demonstrate that the P501S-specific response to the peptide of SEQ ID NO: 712 is restricted to the HLA-B51 class I allele. Molecular cloning and sequence analysis of the HLA-B51 allele from D3326 revealed that the HLA-B51 subtype of D326 is HLA-B51011.

Based on the 10-mer P501S-derived epitope of SEQ ID NO: 712, two 9-mers with the sequences of SEQ ID NO: 714 and 715 were synthesized and tested in Elispot assays for the ability to stimulate two P501S-specific CTL clones derived from line 2A2. The 10-mer peptide of SEQ ID NO: 712, as well as the 9-mer peptide of SEQ ID NO: 715, but not the 9-mer peptide of SEQ ID NO: 714, were capable of stimulating the P501S-specific CTL to produce IFN-gamma. These results demonstrate that the peptide of SEQ ID NO: 715 is a 9-mer P501S-derived epitope recognized by P501S-

specific CTL. The DNA sequence encoding the epitope of SEQ ID NO: 715 is provided in SEQ ID NO: 716.

To identify the class I restricting allele for the P501S-derived peptide of SEQ ID NO: 712 and 715 specific response, each of the HLA B and C alleles were
5 cloned from the donor used in the *in vitro* priming experiment. Sequence analysis indicated that the relevant alleles were HLA-B8, HLA-B51, HLA-Cw01 and HLA-Cw07. Each of these alleles were subcloned into an expression vector and co-transfected together with the P501S gene into VA-13 cells. Transfected VA-13 cells were then tested for the ability to specifically stimulate the P501S-specific CTL in
10 ELISPOT assays. VA-13 cells transfected with P501S and HLA-B51 were capable of stimulating the P501S-specific CTL to secrete gamma-IFN. VA-13 cells transfected with HLA-B51 alone or P501S + the other HLA-alleles were not capable of stimulating the P501S-specific CTL. These results demonstrate that the restricting allele for the P501S-specific response is the HLAB51 allele. Sequence analysis revealed that the
15 subtype of the relevant restricting allele is HLA-B51011.

To determine if the P501S-specific CTL could recognize prostate tumor cells that express P501S, the P501S-positive lines LnCAP and CRL2422 (both expressing "moderate" amounts of P501S mRNA and protein), and PC-3 (expressing low amounts of P501S mRNA and protein), plus the P501S-negative cell line DU-145
20 were retrovirally transduced with the HLA-B51011 allele that was cloned from the donor used to generate the P501S-specific CTL. HLA-B51011- or EGFP-transduced and selected tumor cells were treated with gamma-interferon and androgen (to upregulate stimulatory functions and P501S, respectively) and used in gamma-interferon Elispot assays with the P501S-specific CTL clones 4E5 and 4E7. Untreated
25 cells were used as a control.

Both 4E5 and 4E7 efficiently and specifically recognized LnCAP and CRL2422 cells that were transduced with the HLA-B51011 allele, but not the same cell lines transduced with EGFP. Additionally, both CTL clones specifically recognized PC-3 cells transduced with HLA-B51011, but not the P501S-negative tumor cell line
30 DU-145. Treatment with gamma-interferon or androgen did not enhance the ability of CTL to recognize tumor cells. These results demonstrate that P501S-specific CTL,

generated by *in vitro* whole gene priming, specifically and efficiently recognize prostate tumor cell lines that express P501S.

A naturally processed CD4 epitope of P501S was identified as follows.

CD4 cells specific for P501S were prepared as described above. A series of 16 overlapping peptides were synthesized that spanned approximately 50% of the amino terminal portion of the P501S gene (amino acids 1- 325 of SEQ ID NO: 113). For priming, peptides were combined into pools of 4 peptides, pulsed at 4 μ g/ml onto dendritic cells (DC) for 24 hours, with TNF-alpha. DC were then washed and mixed with negatively selected CD4+ T cells in 96 well U-bottom plates. Cultures were re-stimulated weekly on fresh DC loaded with peptide pools. Following a total of 4 stimulation cycles, cells were rested for an additional week and tested for specificity to APC pulsed with peptide pools using γ -IFN ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool at 4ug/ml or an irrelevant peptide at μ g/ml were used as APC. T cell lines that demonstrated either specific cytokine secretion or proliferation were then tested for recognition of individual peptides that were present in the pool. T cell lines could be identified from pools A and B that recognized individual peptides from these pools.

From pool A, lines AD9 and AE10 specifically recognized peptide 1 (SEQ ID NO: 719), and line AF5 recognized peptide 39 (SEQ ID NO: 718). From pool B, line BC6 could be identified that recognized peptide 58 (SEQ ID NO: 717). Each of these lines were stimulated on the specific peptide and tested for specific recognition of the peptide in a titration assay as well as cell lysates generated by infection of HEK 293 cells with adenovirus expressing either P501S or an irrelevant antigen. For these assays, APC-adherent monocytes were pulsed with either 10, 1, or 0.1 µg/ml individual P501S peptides, and DC were pulsed overnight with a 1:5 dilution of adenovirally infected cell lysates. Lines AD9, AE10 and AF5 retained significant recognition of the relevant P501S-derived peptides even at 0.1 mg/ml. Furthermore, line AD9 demonstrated significant (8.1 fold stimulation index) specific activity for lysates from adenovirus-P501S infected cells. These results demonstrate that high affinity CD4 T cell lines can be generated toward P501S-derived epitopes, and that at least a subset of these T cells specific for the P501S derived sequence of SEQ ID NO: 719 are specific for an epitope that is naturally processed by human cells. The DNA sequences encoding the amino acid sequences of SEQ ID NO: 717-719 are provided in SEQ ID NO: 720-722, respectively.

To further characterize the P501S-specific activity of AD9, the line was cloned using anti-CD3. Three clones, referred to as 1A1, 1A9 and 1F5, were identified that were specific for the P501S-1 peptide (SEQ ID NO: 719). To determine the HLA restriction allele for the P501S-specific response, each of these clones was tested in class II antibody blocking and HLA mismatch assays using proliferation and gamma-interferon assays. In antibody blocking assays and measuring gamma-interferon production using ELISA assays, the ability of all three clones to recognize peptide pulsed APC was specifically blocked by co-incubation with either a pan-class II blocking antibody or a HLA-DR blocking antibody, but not with a HLA-DQ or an irrelevant antibody. Proliferation assays performed simultaneously with the same cells confirmed these results. These data indicate that the P501S-specific response of the clones is restricted by an HLA-DR allele. Further studies demonstrated that the restricting allele for the P501S-specific response is HLA-DRB1501.

EXAMPLE 13**IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS
BY MICROARRAY ANALYSIS**

5 This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

 A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to
10 non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-
15 400) correspond to known sequences, as shown in Table I.

Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-Iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other

normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 623-626. An amino acid sequence encoded by SEQ ID NO: 626 is provided in SEQ ID NO: 627. The cDNA sequence of SEQ ID NO: 623 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 628 and 629.

EXAMPLE 14

IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II
Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

5 Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the
10 Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters
15 (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III
Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

5 The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels
10 of tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes
15 generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

 Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The
20 sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV
Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57

439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that
5 encodes the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

EXAMPLE 15

10 FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above
15 was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-460 represent novel genes. The others (SEQ ID NO: 454-
20 458 and 461-467) correspond to known sequences. Comparison of the determined

cDNA sequence of SEQ ID NO: 461 with sequences in the Genbank database using the BLAST program revealed homology to the previously identified transmembrane protease serine 2 (TMPRSS2). The full-length cDNA sequence for this clone is provided in SEQ ID NO: 751, with the corresponding amino acid sequence being
5 provided in SEQ ID NO: 752. The cDNA sequence encoding the first 209 amino acids of TMPRSS2 is provided in SEQ ID NO: 753, with the first 209 amino acids being provided in SEQ ID NO: 754.

The sequence of SEQ ID NO: 462 (referred to as P835P) was found to correspond to the previously identified clone FLJ13518 (Accession AK023643; SEQ ID
10 NO: 774), which had no associated open reading frame (ORF). This clone was used to search the Geneseq DNA database and matched a clone previously identified as a G protein-coupled receptor protein (DNA Geneseq Accession A09351; amino acid Geneseq Accession Y92365), that is characterized by the presence of seven transmembrane domains. The sequences of fragments between these domains are
15 provided in SEQ ID NO: 778-785, with SEQ ID NO: 778, 780, 782 and 784 representing extracellular domains and SEQ ID NO: 779, 781, 783 and 785 representing intracellular domains. SEQ ID NO: 778-785 represent amino acids 1-28, 53-61, 83-103, 124-143, 165-201, 226-238, 263-272 and 297-381, respectively, of P835P. The full-length cDNA sequence for P835P is provided in SEQ ID NO: 773. The cDNA
20 sequence of the open reading frame for P835P, including stop codon, is provided in SEQ ID NO: 775, with the open reading frame without stop codon being provided in SEQ ID NO: 776 and the corresponding amino acid sequence being provided in SEQ ID NO: 777.

25

EXAMPLE 16

FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P
30 fragment described above. One million colonies were plated on LB/Ampicillin plates.

Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 618.

EXAMPLE 17

PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus, mammalian and yeast cells.

a) Expression of P501S in *E. coli*

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was

cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The
5 resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression
10 was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen
15 Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as
20 Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to
25 aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of
30 the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S

DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The
5 sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C
10 fusion was used for expression in BL21CodonPlus induced by CE6 phage.

A fusion construct comprising a fragment of P501S (amino acids 36-298 of SEQ ID NO: 113) located down-stream of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 705) was prepared as follows. P501S DNA was used to perform PCR using the primers AW042 (SEQ ID NO: 706) and AW053 (SEQ ID NO: 707). AW042 is a sense
15 cloning primer that contains a EcoRI site. AW053 is an antisense primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the EcoRI and Xho I sites. The resulting fusion construct (referred to as Ra12-P501S-E2) was expressed in B834 (DE3) pLys *S. E. coli* host cells in TB media for 2 h at room temperature. Expressed protein
20 was purified by washing the inclusion bodies and running on a Ni-NTA column. The purified protein stayed soluble in buffer containing 20 mM Tris-HCl (pH 8), 100 mM NaCl, 10 mM β -Me and 5% glycerol. The determined cDNA and amino acid sequences for the expressed fusion protein are provided in SEQ ID NO: 708 and 709, respectfully.

25 b) Expression of P501S in Baculovirus

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the

manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

c) Expression of P501S in Mammalian Cells

Full-length P501S (553 amino acids; SEQ ID NO: 113) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The

Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 μ l of GenePorter was diluted in 500 μ l of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 μ g of plasmid DNA that was diluted in 500 μ l of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

d) Expression of P501S in *S. cerevisiae*

P501S was expressed in yeast, directed in membranes, using the yeast α prepro signal sequence. The natural signal sequence and first luminal domain of P501S was deleted in order to conserve the natural positioning of the expressed P501S protein.

Specifically, the α prepro signal sequence of *S. cerevisiae* linked to amino acids 55-553 of SEQ ID NO: 113 with a His tag tail was cloned into the plasmid pRIT15068 with the CUP1 promoter and transfected into *S. cerevisiae* strain Y1790. The Y1790 strain is Leu⁺ and His⁻. Expression of protein was induced by addition of either 500 μ M or 250 μ M of CuSO₄ at 30 °C in minimal medium supplemented with histidine. Cells were harvested 24 hours after induction. Extracts were prepared by growing cells to a concentration of OD600 5.0 in 50 mM citrate phosphate buffer (pH 4.0) plus 130 mM NaCl supplemented with protease inhibitors. Cells were disrupted

using glass beads and centrifuged for 20 min at 15,000 g. The recombinant protein was found to be 100% pellet associated.

Expression of the recombinant protein (molecular weight 63 kD) was demonstrated by Western blot analysis, using the anti-P501S monoclonal antibody 10E-D4-G3 described below. The amino acid sequence of the expressed protein is provided in SEQ ID NO: 792.

Fermentation processes for the production of the α prepro-P501S-His tag recombinant protein in *S. cerevisiae* (strain Y1790 – CUP1 inducible promoter) were evaluated as follows. One hundred μ l of a master seed containing 2.5×10^8 cells/ml of transformed *S. cerevisiae* Y1790 were spread on FSC004AA solid medium. The composition of the FSC004AA medium is as follows: glucose 10 g/l; $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ 0.0002 g/l; folic acid 0.000064 g/l; KH_2PO_4 1 g/l; $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ 0.0004 g/l; Inositol 0.064 g/l; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 0.5 g/l; H_3BO_3 0.0005 g/l; Pyridoxine 0.008 g/l; $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l; $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ 0.00009 g/l; Niacin 0.000032 g/l; $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ 0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l; $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l; $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 0.0004 g/l; $(\text{NH}_4)_2\text{SO}_4$ 5 g/l; agar 18 g/l; Histidine 0.1 g/l.

Two plates were incubated for 26 h at 30 °C. These solid pre-cultures were harvested in 5 ml of liquid medium FSC007AA and 0.5 ml (or 9.3×10^7 cells) of this suspension was used to inoculate 2 liquid pre-cultures.

The composition of the FSC007AA medium is as follows: Glucose 10 g/l; $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ 0.0002 g/l; folic acid 0.000064 g/l; KH_2PO_4 1 g/l; $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ 0.0004 g/l; Inositol 0.064 g/l; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 0.5 g/l; H_3BO_3 0.0005 g/l; Pyridoxine 0.008 g/l; $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l; $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ 0.00009 g/l; Niacine 0.000032 g/l; $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ 0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l; $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l; $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 0.0004 g/l; $(\text{NH}_4)_2\text{SO}_4$ 5 g/l; Histidine 0.1 g/l.

These pre-cultures were run for 20 hours in 2L flasks containing 400 ml of medium FSC007AA in order to obtain an OD of 1.8. The other characteristics of these pre-cultures are as follows: pH 2.8; glucose 2.3 g/L; ethanol 3.4 g/L.

The best timing for liquid pre-cultures for strain Y1790 was determined in preliminary experiments. Liquid pre-cultures containing 400 ml of medium and inoculated with various volumes of Master Seed (0.25, 0.5, 1 or 2 ml) were monitored in order to identify the best inoculum size and timing. Glucose, ethanol, pH, OD and cell number (determined by flow cytometry) were followed between 16 and 23 hours of culture. Glucose exhaustion and maximal biomass were obtained after 20 hour incubation with 0.5 inoculum. These conditions were adopted for transferring the pre-culture into fermentation.

In total, 800ml of pre-culture were used to inoculate a 20 L fermenter containing 5L of medium FSC002AA. Three ml of irradiated antifoam were added before inoculation. The composition of the FSC002AA medium is as follows: $(\text{NH}_4)_2\text{SO}_4$ 6.4 g/l; $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ 2.05 mg/l; folic acid 0.54 mg/l; KH_2PO_4 8.25 g/l; $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ 4.1 mg/l; inositol 540 mg; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 4.69 g/l; H_3BO_3 5.17 m/l; pyridoxine 68 mg/l; $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 0.92 g/l; KI 1.03 mg/l; thiamine 68 mg/l; NaCl 0.06g/l; $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ 0.92 mg/l; Niacine 0.27 mg/l; HCl 1 ml/l; $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ 9.92 mg/l; Riboflavin 0.13 mg/l; $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 0.41 mg/l; Glucose 0.14 g/l; Panthotenate Ca 68 mg/l; $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 4.1 mg/l; Biotin 0.54 mg/l; para-aminobenzoic acid 0.13 mg/l; Histidine 0.3 g/l

The carbon source (glucose) was supplemented by a continuous feeding of FFB004AA medium. The composition of the FFB004AA medium is as follows: glucose 350 g/l; $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$ 5.15 mg/l; folic acid 1.36 mg/l; KH_2PO_4 20.6 g/l; $\text{MnSO}_4 \cdot \text{H}_2\text{O}$ 10.3 mg/l; inositol 1350 mg/l; $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ 11.7 g/l; H_3BO_3 12.9 m/l; pyridoxine 170 mg/l; $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ 2.35 g/l; KI 2.6 mg/l; thiamine 170 g/l; NaCl 0.15 g/l; $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ 2.3 mg/l; niacine 0.67 mg/l; HCl 2.5 ml/l; $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ 24.8 mg/l; riboflavin; 0.33 mg/l; $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ 1.03 mg/l; biotin 1.36 mg/l; panthotenate Ca 170 mg/l; $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ 10.3 mg/l; para-aminobenzoic acid: 0.33 mg/l; histidine 5.35 g/l.

The residual glucose concentration was maintained very low ($\square 50$ mg/L) in order to minimize ethanol production by fermentation. This was achieved by limiting the development of the microorganism using a limited glucose feed rate. The Standard biomass content (OD 80-90) was reached in fermentation after 44 hour growth phase.

CUP1 promoter was then induced by adding 500 μM CuSO_4 in order to

produce P501S antigen. CuSO_4 addition was followed by ethanol accumulation (up to 6 g/L), and the glucose feeding rate was then reduced in order to consume the ethanol. The copper available for the microorganism was monitored by testing Cu ion concentration in the broth supernatant using a spectrophotometric copper assay (DETC method). The fermentation was then supplemented by CuSO_4 throughout the induction phase in order to maintain its concentration between 150 and 250 μM in the supernatant. The biomass reached an OD of 100 at the end of induction. Cells were harvested after 8 hours of induction.

Cell homogenate was prepared and analysed by SDS-PAGE and Western Blot using standard protocols. A major protein band with the expected molecular weight of 62KD was detected by Western blot using anti-P501S monoclonal antibodies. Western blot analysis also showed that the major 62KD band was progressively produced from 30 minutes of induction on, and reached a maximum after 3 hours. No more antigen seemed to be produced between 3 and 12 hours of induction.

The number of passages through a French Press necessary to extract all the antigen from the cells was evaluated. One, three and five passages were tested and total cell lysates, supernatants and pellets of cell lysates were analysed by Western blot. Three passages through a French Press were sufficient to completely extract the antigen. The antigen was present in the insoluble fraction.

20

e) Expression of P703P in Baculovirus

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with restriction endonucleases Xba I and Hind III. The resulting restriction fragment (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

30

e) Expression of P788P in *E. Coli*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 672 and 673). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 674, with the corresponding amino acid sequence being provided in SEQ ID NO: 675.

f) Expression of P510S in *E. Coli*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal end, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 677 and 678, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and

vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction
5 the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin +
10 chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 679 and 682,
15 respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were
20 those shown in SEQ ID NO: 685 and 686, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 685 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 686 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL
25 competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin
30 and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at

37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-C construct are shown in SEQ ID NO: 680 and 683, respectively.

5 The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was amplified by PCR using the primers shown in SEQ ID NO: 687 and 688. The primer of SEQ ID NO: 687 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 688 is an antisense primer with an added XhoI site
10 for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing
15 confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3
20 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P501S-E3 construct are provided in SEQ ID NO: 681 and 684, respectively.

g) Expression of P775S in *E. Coli*

25 The antigen P775P contains multiple open reading frames (ORF). The third ORF, encoding the protein of SEQ ID NO: 483, has the best emotif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 689 and the anti-sense PCR primer of SEQ ID NO: 690. The PCR amplified fragment of P775P and

Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after
5 induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 691 and 692, respectively.

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H) EXPRESSION OF A P703P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P703P was prepared by PCR using the primers of SEQ ID NO: 693 and 694. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag
15 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P703P are provided in SEQ ID NO: 695 and 696, respectively.

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I) EXPRESSION OF A P705P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P705P was prepared by PCR using the primers of SEQ ID NO: 697 and 698. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag
25 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P705P are provided in SEQ ID NO: 699 and 700, respectively.

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J) EXPRESSION OF A P711P HIS TAG FUSION PROTEIN IN E. COLI

The cDNA for the coding region of P711P was prepared by PCR using the primers of SEQ ID NO: 701 and 702. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco2I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P711P are provided in SEQ ID NO: 703 and 704, respectively.

EXAMPLE 18**PREPARATION AND CHARACTERIZATION OF ANTIBODIES
AGAINST PROSTATE-SPECIFIC POLYPEPTIDES****a) Preparation and Characterization of Polyclonal Antibodies against P703P,
P504S and P509S**

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run

through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialled after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room

temperature for 2 hours. Plates were washed 6 times with PBS/0.01 % Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H₂SO₄ and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

b) Preparation and Characterization of Antibodies against P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were

generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

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Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant ($\mu\text{g/ml}$)
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1 $\mu\text{g/ml}$, followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-

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LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with
5 P501S or HLA-B8 as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines
10 Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically
15 recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells
20 were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145
25 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L) Affinipure F(ab') fragment (Jackson ImmunoResearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from

these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

c) Preparation and Characterization of Antibodies against P503S

10. A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at
- 15 Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

5 In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well
10 microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was
15 followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with
20 supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds
25 to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to
30 cell surface epitopes. Cells stably transfected with a control plasmid were employed as

a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur
5 fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder,
10 ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall
15 bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with
20 each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa
25 species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

d) Preparation and Characterization of Antibodies against P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P

protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptrl attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk^{-/-} cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with

recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

e) Preparation and Characterization of Antibodies against P504S

Full-length P504S (SEQ ID NO: 108) was expressed and purified from bacteria essentially as described above for P501S and employed to raise rabbit monoclonal antibodies using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). The anti-P504S monoclonal antibody 13H4 was shown by Western blot to bind to both expressed recombinant P504S and to native P504S in tumor cells.

Immunohistochemical studies using 13H4 to assess P504S expression in various prostate tissues were performed as described above. A total of 104 cases, including 65 cases of radical prostatectomies with prostate cancer (PC), 26 cases of prostate biopsies and 13 cases of benign prostate hyperplasia (BPH), were stained with the anti-P504S monoclonal antibody 13H4. P504S showed strongly cytoplasmic granular staining in 64/65 (98.5%) of PCs in prostatectomies and 26/26 (100%) of PCs in prostatic biopsies. P504S was stained strongly and diffusely in carcinomas (4+ in 91.2% of cases of PC; 3+ in 5.5%; 2+ in 2.2% and 1+ in 1.1%) and high grade prostatic intraepithelial neoplasia (4+ in all cases). The expression of P504S did not vary with Gleason score. Only 17/91 (18.7%) of cases of NP/BPH around PC and 2/13 (15.4%) of BPH cases were focally (1+, no 2+ to 4+ in all cases) and weakly positive for P504S in large glands. Expression of P504S was not found in small atrophic glands, postatrophic hyperplasia, basal cell hyperplasia and transitional cell metaplasia in either biopsies or

prostatectomies. P504S was thus found to be over-expressed in all Gleason scores of prostate cancer (98.5 to 100% of sensitivity) and exhibited only focal positivities in large normal glands in 19/104 of cases (82.3% of specificity). These findings indicate that P504S may be usefully employed for the diagnosis of prostate cancer.

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EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

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This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

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The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

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Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519,

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which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed, incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1

complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng - 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the

peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

In further studies, mouse monoclonal antibodies were raised against amino acids 296 to 322 to P501S, which are predicted to be in an extracellular domain. A/J mice were immunized with P501S/adenovirus, followed by subsequent boosts with an *E. coli* recombinant protein, referred to as P501N, that contains amino acids 296 to 322 of P501S, and with peptide 296-322 (SEQ ID NO: 755) coupled with KLH. The mice were subsequently used for splenic B cell fusions to generate anti-peptide hybridomas. The resulting 3 clones, referred to as 4F4 (IgG1,kappa), 4G5 (IgG2a,kappa) and 9B9 (IgG1,kappa), were grown for antibody production. The 4G5 mAb was purified by passing the supernatant over a Protein A-sepharose column,

followed by antibody elution using 0.2M glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8, and buffer exchanged into PBS.

For ELISA analysis, 96 well plates were coated with P501S peptide 296-322 (referred to as P501-long), an irrelevant P775 peptide, P501S-N, P501TR2, P501S-long-KLH, P501S peptide 306-319 (referred to as P501-short)-KLH, or the irrelevant peptide 2073-KLH, all at a concentration of 2 ug/ml and allowed to incubate for 60 minutes at 37 °C. After coating, plates were washed 5X with PBS + 0.1% Tween and then blocked with PBS, 0.5% BSA, 0.4% Tween20 for 2 hours at room temperature. Following the addition of supernatants or purified mAb, the plates were incubated for 60 minutes at room temperature. Plates were washed as above and donkey anti-mouse IgHRP-linked secondary antibody was added and incubated for 30 minutes at room temperature, followed by a final washing as above. TMB peroxidase substrate was added and incubated 15 minutes at room temperature in the dark. The reaction was stopped by the addition of 1N H₂SO₄ and the OD was read at 450 nM. All three hybrid clones secreted mAb that recognized peptide 296-322 and the recombinant protein P501N.

For FACS analysis, HEK293 cells were transiently transfected with a P501S/VR1012 expression constructs using Fugene 6 reagent. After 2 days of culture, cells were harvested and washed, then incubated with purified 4G5 mAb for 30 minutes on ice. After several washes in PBS, 0.5% BSA, 0.01% azide, goat anti-mouse Ig-FITC was added to the cells and incubated for 30 minutes on ice. Cells were washed and resuspended in wash buffer including 1% propidium iodide and subjected to FACS analysis. The FACS analysis confirmed that amino acids 296-322 of P501S are in an extracellular domain and are cell surface expressed.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server

(<http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl>) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al.* *Science* 274:1371-1374, 1996 and Berthon *et al.* *Am. J. Hum. Genet.* 62:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

EXAMPLE 20

REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

10

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

15

Cells from the prostate tumor cell line LNCaP were plated at 1.5×10^6 cells/T75 flask (for RNA isolation) or 3×10^5 cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

20

25

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The filter was then prehybridized with Church's Buffer (250 mM Na_2HPO_4 , 70 mM H_3PO_4 , 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was

30

labeled with ^{32}P using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 0.001 M Na_2EDTA), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found to increase in response to androgen treatment.

10

EXAMPLE 20

PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP

cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

5 The fusion FOPP was expressed as a single recombinant protein in *E. coli* as follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml
10 chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the
15 cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl
20 pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing
25 FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN
PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

5 Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the TaqmanTM procedure using both gene specific primers and probes to determine the levels of gene expression.

10 Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0
15 and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the TaqmanTM procedure but extending to 50 cycles using
20 forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and β -actin signal. The remaining 2 samples had no detectable β -actin or P501S. No P501S signal was observed in the four normal blood samples tested.

EXAMPLE 22

EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGENS P703P AND P501S IN
SCID MOUSE-PASSAGED PROSTATE TUMORS

25 When considering the effectiveness of antigens in the treatment of
30 prostate cancer, the continued presence of the antigens in tumors during androgen

ablation therapy is important. The presence of the prostate-specific antigens P703P and P501S in prostate tumor samples grown in SCID mice in the presence of testosterone was evaluated as follows.

Two prostate tumors that had metastasized to the bone were removed from patients, implanted into SCID mice and grown in the presence of testosterone. Tumors were evaluated for mRNA expression of P703P, P501S and PSA using quantitative real time PCR with the SYBR green assay method. Expression of P703P and P501S in a prostate tumor was used as a positive control and the absence in normal intestine and normal heart as negative controls. In both cases, the specific mRNA was present in late passage tumors. Since the bone metastases were grown in the presence of testosterone, this implies that the presence of these genes would not be lost during androgen ablation therapy.

EXAMPLE 23

ANTI-P503S MONOCLONAL ANTIBODY INHIBITS TUMOR GROWTH *IN VIVO*

The ability of the anti-P503S monoclonal antibody 20D4 to suppress tumor formation in mice was examined as follows.

Ten SCID mice were injected subcutaneously with HEK293 cells that expressed P503S. Five mice received 150 micrograms of 20D4 intravenously at day 0 (time of tumor cell injection), day 5 and day 9. Tumor size was measured for 50 days. Of the five animals that received no 20D4, three formed detectable tumors after about 2 weeks which continued to enlarge throughout the study. In contrast, none of the five mice that received 20D4 formed tumors. These results demonstrate that the anti-P503S Mab 20D4 displays potent anti-tumor activity *in vivo*.

EXAMPLE 24

CHARACTERIZATION OF A T CELL RECEPTOR CLONE FROM A P501S-SPECIFIC T CELL CLONE

T cells have a limited lifespan. However, cloning of T cell receptor (TCR) chains and subsequent transfer essentially enables infinite propagation of the T

cell specificity. Cloning of tumor-antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share the TCR MHC-restricting allele. Such T cells could then be expanded and used in adoptive transfer settings to introduce the tumor antigen specificity into patients carrying tumors that express the antigen. T cell receptor alpha and beta chains from a CD8 T cell clone specific for the prostate-specific antigen P501S were isolated and sequenced as follows.

Total mRNA from 2×10^6 cells from CTL clone 4E5 (described above in Example 12) was isolated using Trizol reagent and cDNA was synthesized. To determine Va and Vb sequences in this clone, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb7 subfamily. Furthermore, using cDNA generated from the clone, the Va sequence expressed was determined to be Va6. To clone the full TCR alpha and beta chains from clone 4E5, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows: TCR Valpha-6 5'(sense): GGATCC---GCCGCCACC---ATGTCACCTTTCTAGCCTGCT (SEQ ID NO: 756) BamHI site Kozak TCR alpha sequence TCR alpha 3' (antisense): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 757) SalI site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC---GCCGCCACC---ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 758) BamHI site Kozak TCR alpha sequence TCR beta 3' (antisense): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 759) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the above primers, employing the proofreading thermostable polymerase PWO (Roche, Nutley, NJ).

The resultant specific bands (approx. 850 bp for alpha and approx. 950 for beta) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were submitted

for sequencing. The sequencing reactions demonstrated the cloning of full-length TCR alpha and beta chains with the determined cDNA sequences for the Vb and Va chains being shown in SEQ ID NO: 760 and 761, respectively. The corresponding amino acid sequences are shown in SEQ ID NO: 762 and 763, respectively. The Va sequence was
5 shown by nucleotide sequence alignment to be 99% identical (347/348) to Va6.2, and the Vb to be 99% identical to Vb7 (336/338),

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,
10 various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788 under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-

375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(b) sequences having at least 70% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(c) sequences having at least 90% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-

629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

- (d) sequences encoded by a polynucleotide of claim 1;
- (e) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (f) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.

8. The fusion protein of claim 7, wherein the fusion protein comprises a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 682, 692, 695, 699, 703 and 709; and

(b) sequences encoded by SEQ ID NO: 679, 691, 696, 700, 704 and 708.

9. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 or 786-788 under moderately stringent conditions.

10. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;
(b) polynucleotides according to claim 1; and
(c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

11. An isolated T cell population, comprising T cells prepared according to the method of claim 10.

12. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1;
- (c) antibodies according to claim 5;
- (d) fusion proteins according to claim 7;
- (e) T cell populations according to claim 11; and
- (f) antigen presenting cells that express a polypeptide according to claim 2.

13. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 12.

14. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 12.

15. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 9;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

16. A diagnostic kit comprising at least one oligonucleotide according to claim 9.

17. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

18. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells,

thereby inhibiting the development of a cancer in the patient.

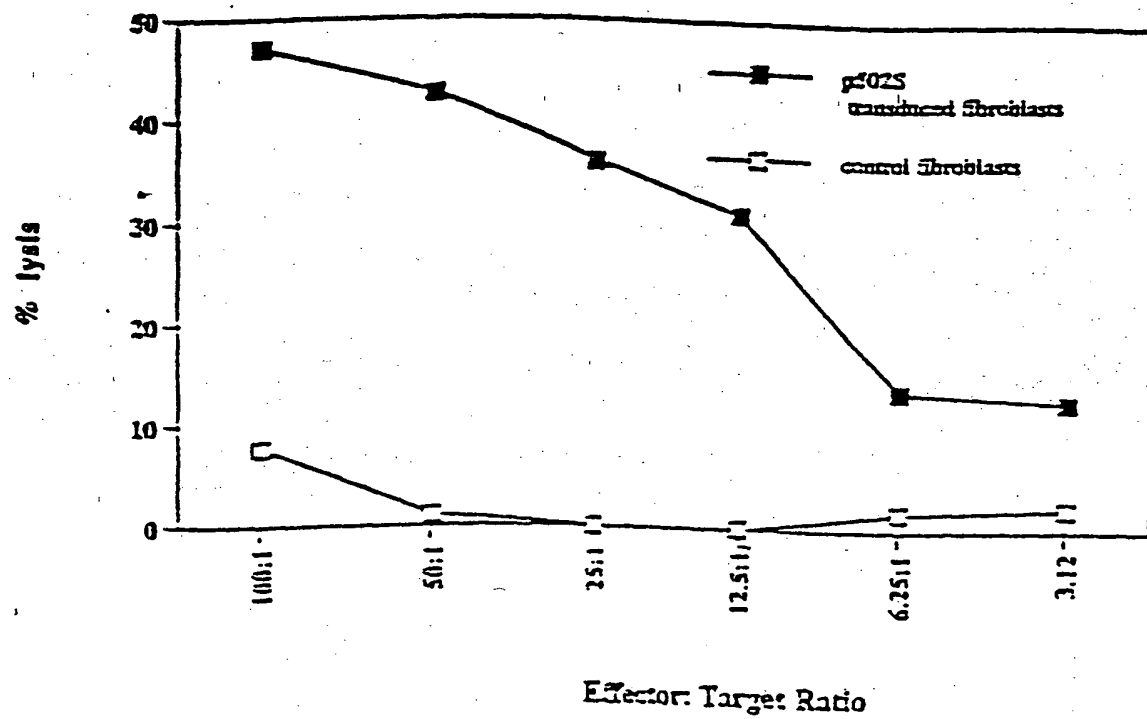


Fig. 1

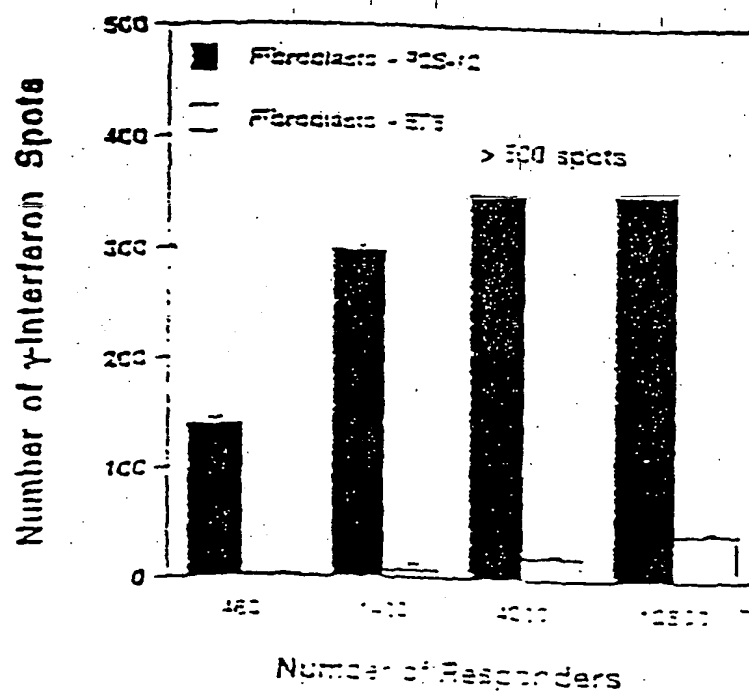


Fig. 2A

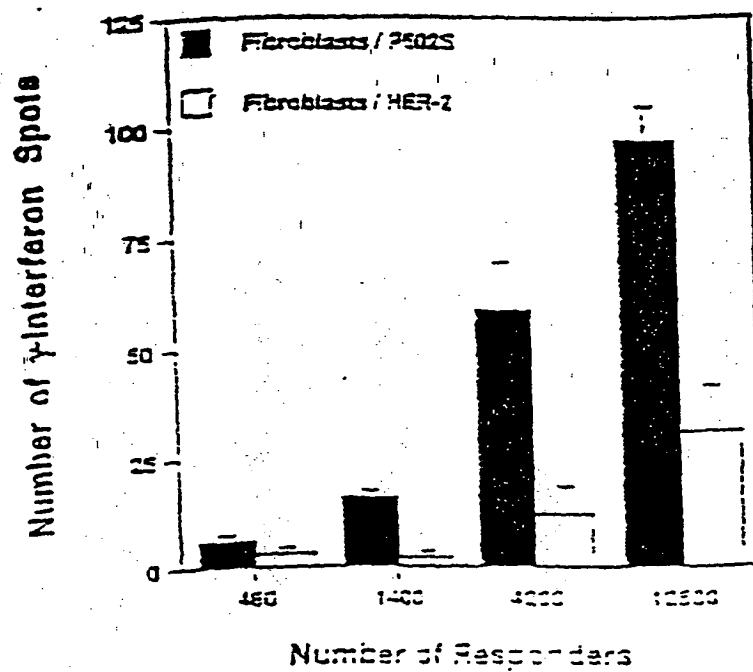


Fig. 25

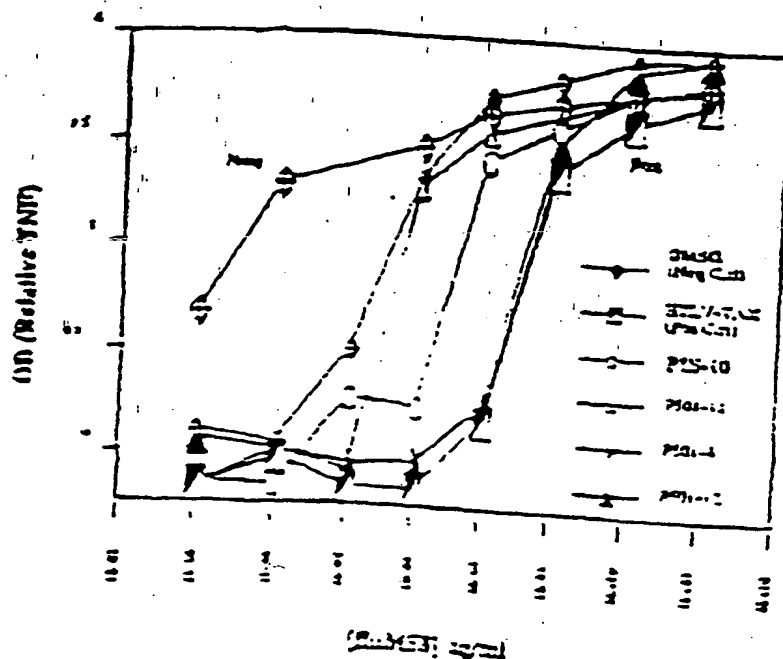


Fig. 3

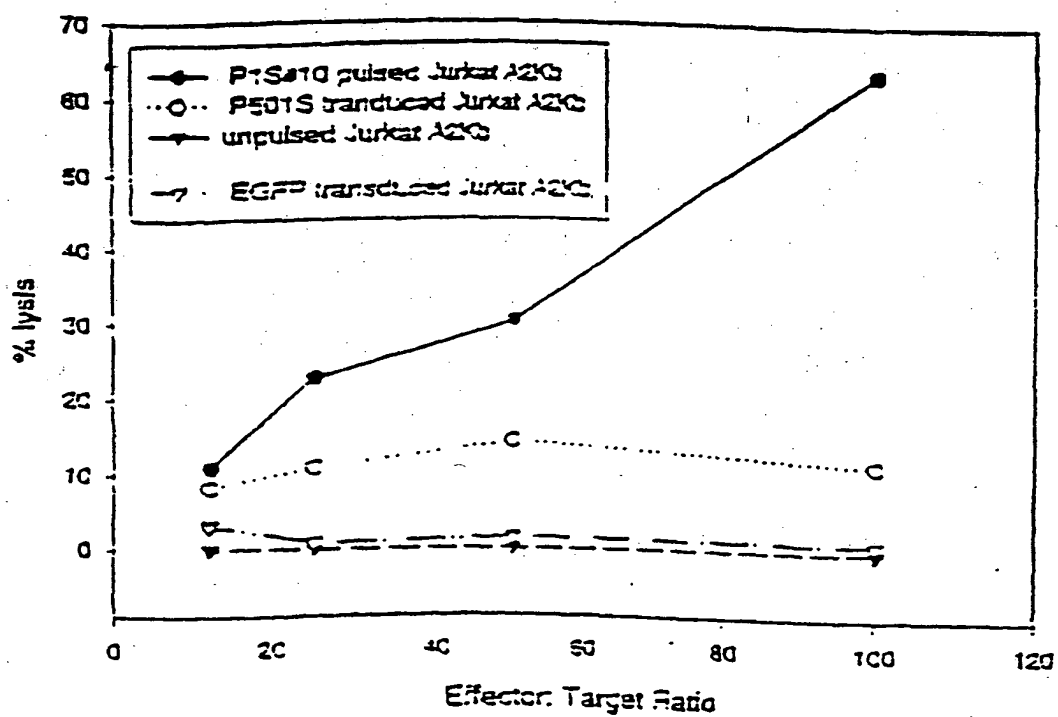


Fig. 4

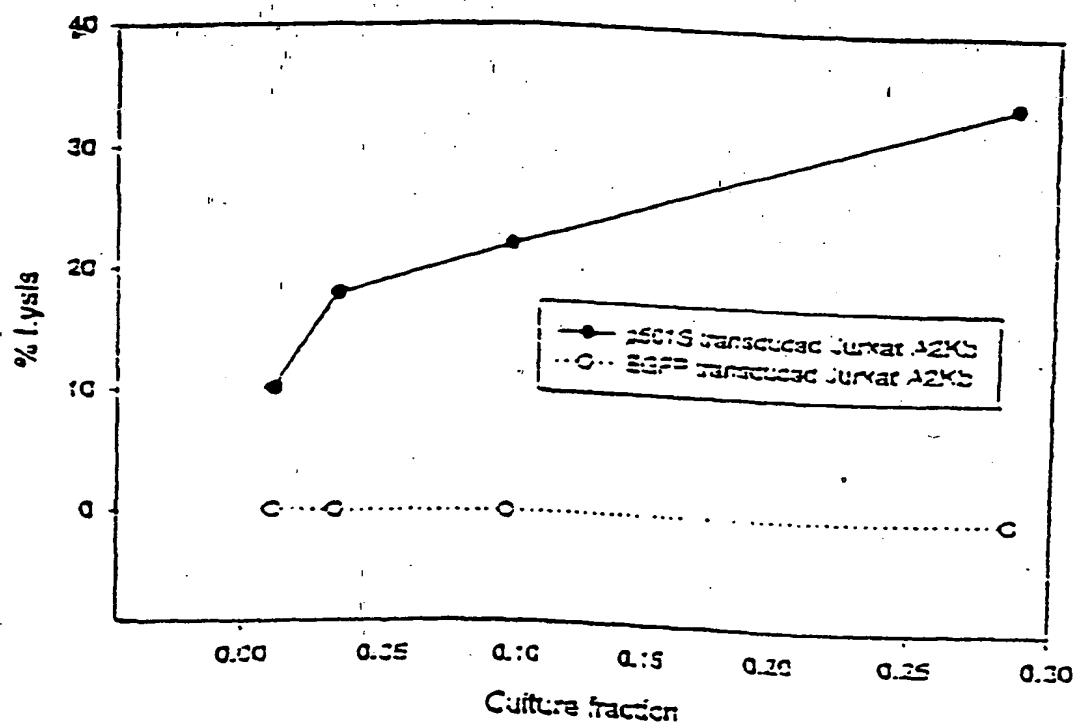


Fig. 5

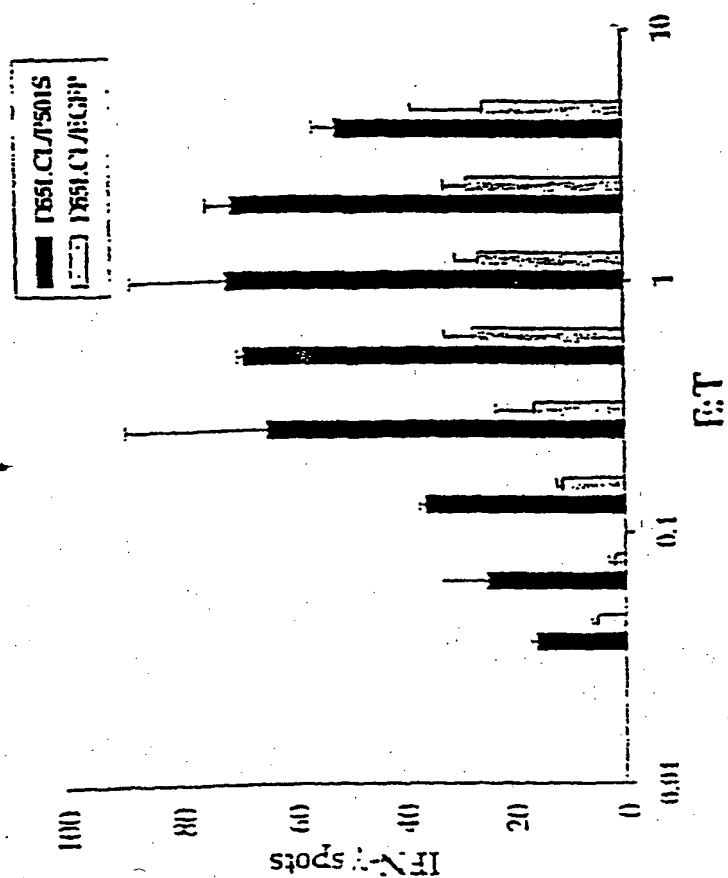


Fig. 6B

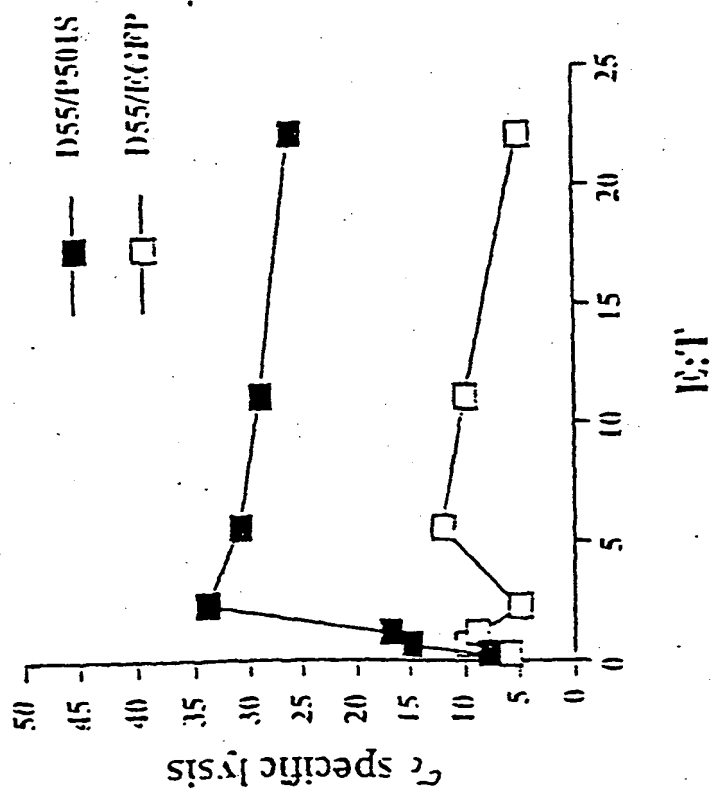
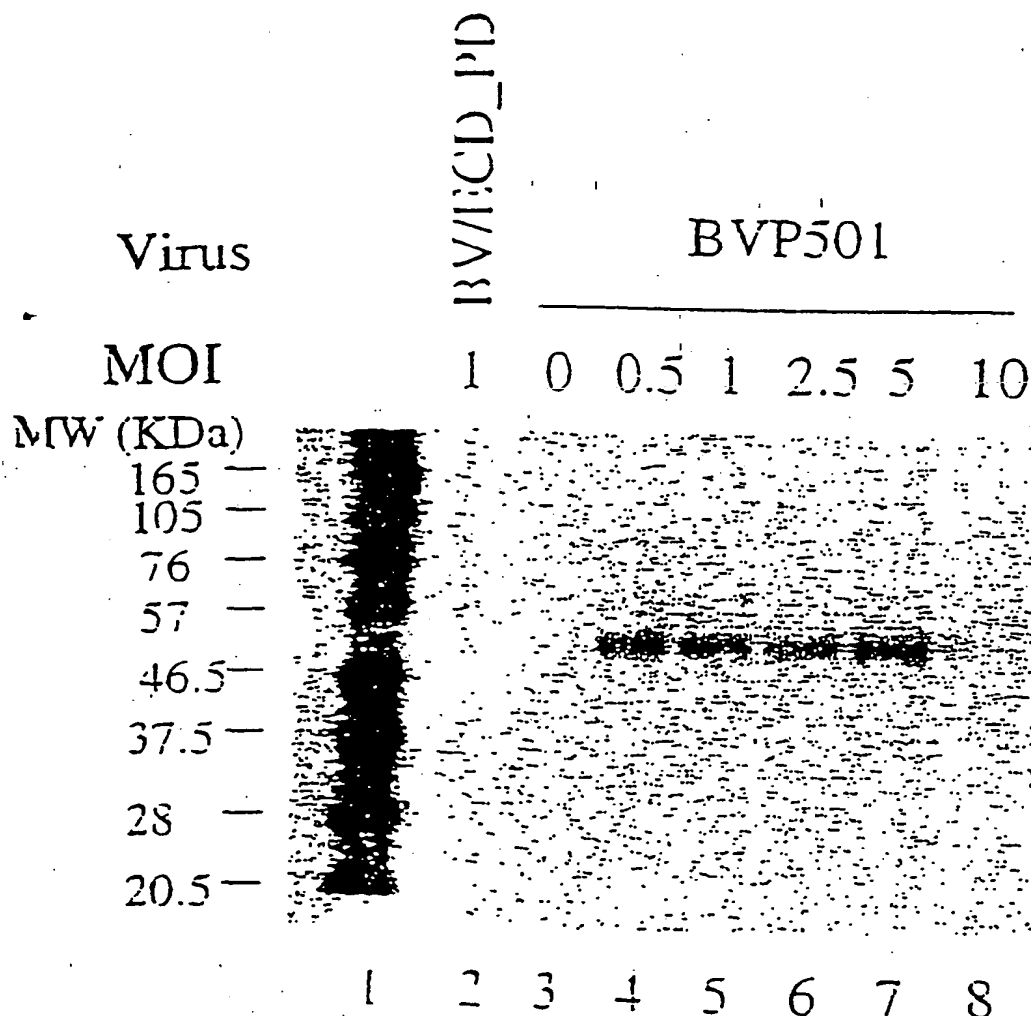


Fig. 6A

Expression of P501S by the Baculovirus Expression System



0.6 million high 5 cells in 6-well plate were infected with an unrelated control virus BV/ECD_PD (lane 2), without virus (lane 3), or with recombinant baculovirus for P501S at different MOIs (lane 4-8). Cell lysates were run on SDS-PAGE under the reducing conditions and analyzed by Western blot with a monoclonal antibody against P501S (P501S-10E3-G4D3). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

Fig. 7

Figure 8. Mapping of the epitope recognized by 10E3-G4-D3

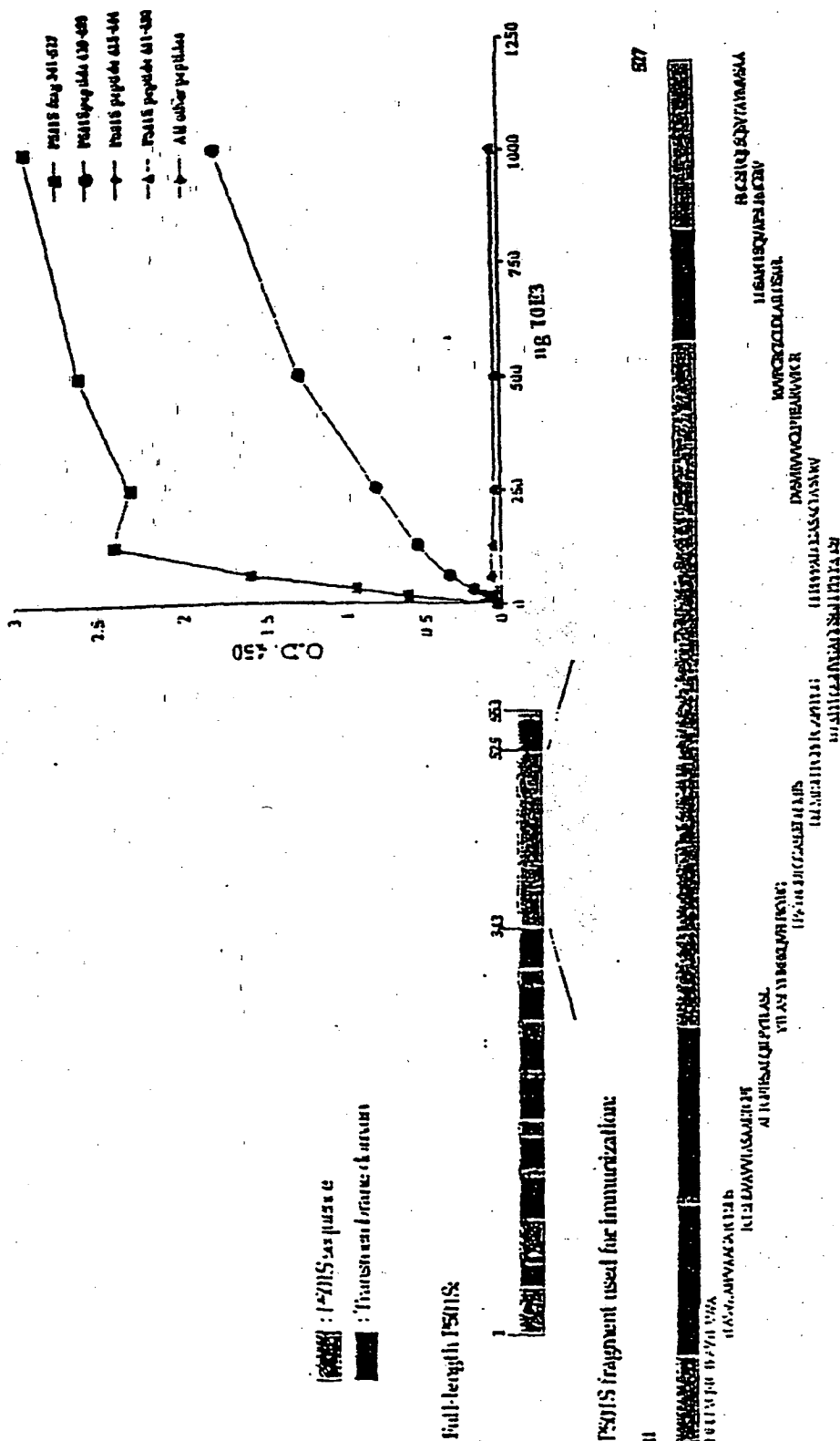


Fig. 8

Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

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Underlined sequence: Predicted transmembrane domain; **Bold sequence**: Predicted extracellular domain;

Italic sequence: Predicted intracellular domain. Sequence in bold/underlined: used to generate polyclonal rabbit serum

Localization of domains predicted using IMMTPP (C.R. Tusnady and I. Simon (1998) Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction. J. Mol. Biol. 283, 489-506.

Genomic Map of (5) Corixa Candidate Genes

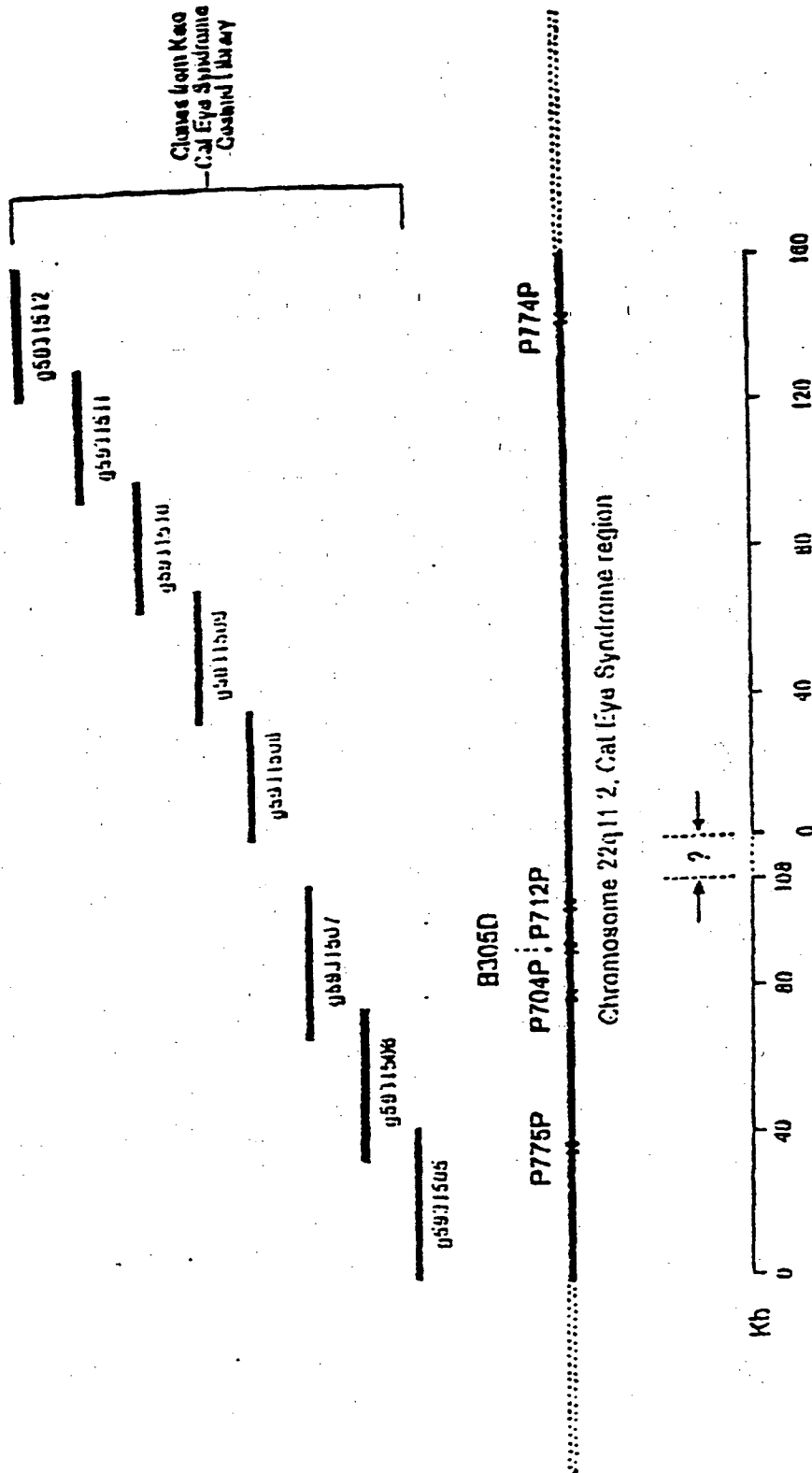


Fig. 10

FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity

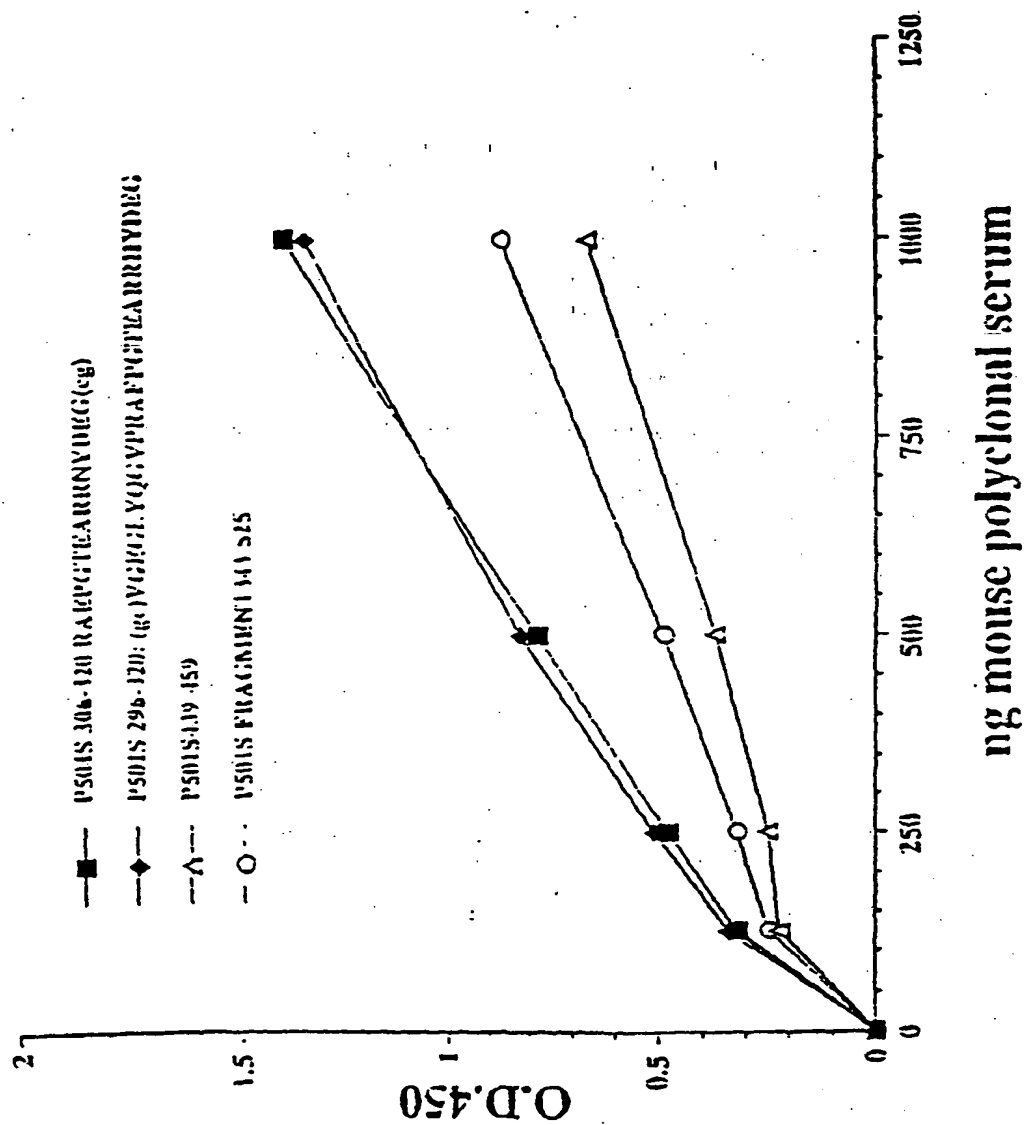


Fig. 11

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 Harlocker, Susan L.
 Jiang, Yuqi
 Reed, Steven G.
 Kalos, Michael D.
 Fanger, Gary R.
 Retter, Marc W.
 Stolk, John A.
 Day, Craig H.
 Skeiky, Yasir A.W.
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agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtanggtg	agtcctcaaa	atccgtatag	ttggtgaagc	cacagcactt	gagccctttc	240
atggtggtgt	tcacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	ggaagtgtct	agccattgtg	gtgtacacca	aggcgaccac	360
agcagctgcn	acctcagcaa	tgaagatgan	gaggangatg	aagaagaacg	tcncgagggc	420
acacttgctc	tcagtcttan	caccatanca	gcccntgaaa	accaananca	aagaccacna	480
cncgggtgc	gatgaagaaa	tnaccccneg	ttgacaaact	tgcatggcac	tggganccac	540
agtggccnna	aaaatcttca	aaaaggatgc	cccatcnatt	gaccccccaa	atgcccactg	600
ccaacagggg	ctgccccacn	cncnnaacga	tgancnatt	gnacaagatc	tncntgggtct	660
tnatnaacnt	gaaccctgcn	tngtggctcc	tgttcaggnc	cnnggcctga	cttctnaann	720
aangaactcn	gaagncccca	cngganannc	g			751

<210> 13
 <211> 729
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(729)

<223> n = A,T,C or G

<400> 13

gagccaggcg	tccctctgcc	tgcccactca	gtggcaacac	ccgggagctg	ttttgtcctt	60
tgtggancct	cagcagtncc	ctctttcaga	actcantgcc	aagancctg	aacaggagcc	120
accatgcagt	gcttcagctt	cattaagacc	atgatgatcc	tcttcaattt	gctcatcttt	180
ctgtgtgggtg	cagccctgtt	ggcagtgggc	atctgggtgt	caatcgatgg	ggcatccttt	240
ctgaagatct	tggggccact	gtcgtccagt	gccatgcagt	ttgtcaacgt	gggctacttc	300
ctcatcgag	ccggcggtgt	ggtcttagct	ctagggtttcc	tgggctgcta	tggtgctaag	360
actgagagca	agtgtgccct	cgtgacgttc	ttcttcatcc	tcctcctcat	cttcattgct	420
gaggttgcaa	tgtctgtggc	gccttggtgt	acaccacaat	ggctgagcac	ttcctgacgt	480
tgtgtgtaat	gcctgccatc	aanaaaagat	tatgggttcc	caggaanact	tcaactcaagt	540
gttggaacac	caccatgaaa	gggctcaagt	gctgtggctt	cnnccaacta	tacggatttt	600
gaagantcac	ctacttcaaa	gaaaanagt	cctttccccc	atttctgttg	caattgacaa	660
acgtcccca	cacagccaat	tgaaaacctg	cacccaacc	aaanggtcc	ccaaccanaa	720
attnaagg						729

<210> 14

<211> 816

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(816)

<223> n = A,T,C or G

<400> 14

tgctcttct	caaagttgtt	cttgttgcca	taacaaccac	cataggtaaa	gcgggcgcag	60
tgttcgctga	aggggttgta	gtaccagcgc	gggatgctct	ccttgacagag	tcctgtgtct	120
ggcaggtcca	cgagtgccc	tttgtcactg	gggaaatgga	tgcgctggag	ctcgtcaaa	180
ccactcgtgt	atttttcaca	ggcagcctcg	tcggagcgcg	cggggcagtt	gggggtgtct	240
tcacactcca	ggaaactgtc	natgcagcag	ccattgctgc	agcgggaactg	ggtgggctga	300
cangtgccag	agcacactgg	atggcgccct	tccatgnnan	gggccctgng	ggaaagtccc	360
tgancccan	anctgcctct	caaangcccc	accttgacac	ccccgacagg	ctagaatgga	420
atcttcttcc	cgaaaggtag	ttnttcttgt	tgcccaancc	anccccntaa	acaaactctt	480
gcanatctgc	tccngggggg	tontantacc	ancgtgggaa	aagaacccca	ggcngcgaac	540
caancttgtt	tggatncgaa	gcnataatct	ncntttctgc	ttggtggaca	gcaccantna	600
ctgtnnanct	ttagnccntg	gtcctontgg	ggtgnncttg	aacctaatcn	ccnntcaact	660
gggacaaggt	aantngccnt	cctttnaatt	cccnancntn	ccccctgggt	tgggggtttt	720
cncnctcta	ccccagaaan	ncctgtgtcc	cccccaacta	ggggccnaaa	ccnnttnttc	780
cacaacctn	ccccaccac	gggttcngnt	ggttng			816

<210> 15

<211> 783

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(783)

<223> n = A,T,C or G

<400> 15

ccaaggcctg	ggcaggcata	nacttgaagg	tacaacccca	ggaaccctg	gtgctgaagg	60
atgtggaaaa	cacagattgg	cgctactgc	ggggtgacac	ggatgtcagg	gtagagagga	120
aagacccaaa	ccaggtggaa	ctgtggggac	tcaaggaang	cacctacctg	ttccagctga	180
cagtgactag	ctcagaccac	ccagaggaca	cggccaacgt	cacagtcact	gtgctgtcca	240
ccaagcagac	agaagactac	tgcctcgcac	ccaacaangt	gggtcgctgc	cggggtcttt	300
tcccacgctg	gtactatgac	cccacggagc	agatctgcaa	gagtttcgtt	tatggagggt	360
gcttgggcaa	caagaacaac	taccttcggg	aagaagagtg	cattctance	tgtcnggggtg	420
tgcaaggtgg	gcctttgana	ngcanctctg	gggtcangc	gactttcccc	cagggccctt	480
ccatggaaa	gcgccatcca	ntgttctctg	gcacctgtca	gccaccag	ttccgtgca	540
ncaatggctg	ctgcatcnac	antttcctng	aattgtgaca	acaaccccca	ntgcccccaa	600
ccctcccaac	aaagcttccc	tgttnaaaaa	tacnccantt	ggcttttnac	aaacnccogg	660
cncctcctt	ttcccnntn	aacaaagggc	nctngccttt	gaactgcccn	aaccnnggaa	720
tctnccnngg	aaaaantncc	ccccctggtt	cctnnaancc	cctccncaaa	antncccccc	780
ccc						783

<210> 16

<211> 801

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(801)

<223> n = A,T,C or G

<400> 16

gccccaatc	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtaggggtg	agtcctcaaa	atccgtatag	ttggtgaagc	cacagcactt	gagccctttc	240
atgggtgggtg	tccacacttg	agtgaagtct	tcttgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	gaagtgtctc	gccattgtgg	tgtacaccaa	ggcgaccaca	360
gcagctgcaa	cctcagcaat	gaagatgagg	aggaggatga	agaagaacgt	cncgagggca	420
cacttgctct	ccgtcttagc	accatagcag	cccangaaac	caagagcaaa	gaccacaacg	480
ccngctgcga	atgaaagaaa	ntaccacacg	tgacaaaactg	catggccact	ggacgacagt	540
tggcccgaa	atcttcagaa	aagggatgcc	ccatcgattg	aacacccana	tgcccactgc	600
cnacagggct	gcncncncn	gaaagaatga	gccattgaag	aaggatcctc	ntggtcttaa	660
tgaactgaaa	ccntgcatgg	tgccccctgt	tcagggtctc	tggcagtgaa	ttctganaaa	720
aaggaacngc	ntnagcccc	ccaaangana	aaacaccccc	gggtgttgcc	ctgaattggc	780
ggccaaggan	ccctgccccn	g				801

<210> 17

<211> 740

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(740)

<223> n = A,T,C or G

<400> 17

gtgagagcca	ggcgtccctc	tgcttgccca	ctcagtgcca	acacccggga	gctgttttgt	60
cctttgtgga	gcctcagcag	ttccctcttt	cagaactcac	tgccaagagc	cctgaacagg	120
agccaccatg	cagtgtctca	gcttcattaa	gaccatgatg	atcctcttca	atttgctcat	180
ctttctgtgt	ggtgcagccc	tgttggcagt	gggcatctgg	gtgtcaatcg	atggggcatc	240
ctttctgaag	atcttcgggc	cactgtcgtc	cagtgccatg	cagtttgtca	acgtgggcta	300

cttcctcatc	gcagccggcg	ttgtggtcct	tgctcttggt	ttcctgggct	gctatggtgc	360
taagacggag	agcaagtgtg	cctcgtgac	gttcttcttc	atcctcctcc	tcattctcat	420
tgctgaagtt	gcagctgctg	tggtcgccct	ggtgtacacc	acaatggctg	aaccattcct	480
gacgttgctg	gtantgcctg	ccatcaanaa	agattatggg	ttcccaggaa	aaattcactc	540
aantntggaa	caccnccatg	aaaagggctc	caattttctgn	tggtctcccc	aactataccg	600
gaattttgaa	agantcncct	tacttccaaa	aaaaaanant	tgcttttnc	cccnttctgt	660
tgcaatgaaa	acntcccaan	acngccaatn	aaaacctgcc	cnnncaaaaa	ggntcncaaa	720
caaaaaaant	nnaagggttn					740

<210> 18

<211> 802

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(802)

<223> n = A,T,C or G

<400> 18

ccgctgggtg	cgctgggtcca	gngnagccac	gaagcacgtc	agcatacaca	gcctcaatca	60
caaggtcttc	cagctgcgcg	acattacgca	gggcaagagc	ctccagcaac	actgcatatg	120
ggatacactt	tacttttagca	gccaggggtga	caactgagag	gtgtcgaagc	ttattcttct	180
gagcctctgt	tagtggagga	agattccggg	cttcagctaa	gtagtcagcg	tatgtcccat	240
aagcaaacac	tgtgagcagc	cgggaaggtag	aggcaaaagtc	actctcagcc	agctctctaa	300
cattgggcat	gtccagcagt	tctccaaaca	cgtagacacc	agnggcctcc	agcacctgat	360
ggatgagtgt	ggccagcgct	gcccccttgg	ccgacttggc	taggagcaga	aattgctcct	420
ggttctgccc	tgtcaccttc	acttccgcac	tcatactgc	actgagtgtg	ggggacttgg	480
gctcaggatg	tccagagacg	tggttccgcc	ccctcnctta	atgacaccgn	ccanncaacc	540
gtcggctccc	gcccantng	ttcgtcgtnc	ctgggtcagg	gtctgctggc	cnctacttgc	600
aancttcgtc	nggcccattg	aattcaccnc	accggaactn	gtangatcca	ctnnttctat	660
aaccggnccg	caccgcnnnt	ggaactccac	tcttnttnc	tttacttgag	ggttaaggtc	720
acccttnncc	ttaccttggg	ccaaaccntn	ccntgtgtcg	anatngtnaa	tcnggnccna	780
tnccanccnc	atangaagcc	ng				802

<210> 19

<211> 731

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(731)

<223> n = A,T,C or G

<400> 19

cnaagcttcc	aggtnacggg	ccgcnaaanc	tgaccnagg	tancanaang	cagnccggcg	60
gagcccaacc	tcacgnngng	ngtctttat	nggagggggc	ggagccacat	cnctggacnt	120
cntgacccca	actcccncc	ncncantgca	gtgatgagt	cagaactgaa	ggtnacgtgg	180
caggaaccaa	gancaaannc	tgctccnntc	caagtcggcn	nagggggcg	ggctggccac	240
gcncatccnt	cnagtgtgn	aaagcccn	cctgtctact	tgtttgaga	acngcnnga	300
catgcccagn	gttanataac	ngcngagag	tnantttgcc	tctcccttcc	ggctgcgan	360
cgngtntgct	tagnggacat	aacctgacta	cttaactgaa	cccnngaate	tnccnccct	420
ccactaagct	cagaacaaaa	aacttcgaca	ccactcantt	gtcacctgnc	tgctcaagta	480
aagtgtaccc	catncccaat	gtntgctnga	ngctctgncc	tgcnttangt	tcggctctgg	540
gaagacctat	caattnaagc	tatgtttctg	actgcctctt	gctccctgna	acaancnacc	600
cnncnntcca	agggggggnc	ggcccccaat	ccccccaacc	ntnaattnan	tttancccn	660
ccccnggcc	cggcctttta	cnancntcnn	nnacngggna	aaaccnnngc	tttncccaac	720

nnaatccncc t

731

<210> 20

<211> 754

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(754)

<223> n = A, T, C or G

<400> 20

tttttttttt	tttttttttt	taaaaacccc	ctccattnaa	tgnaaaacttc	cgaaattgtc	60
caaccacctc	ntccaaatnn	ccntttccgg	gnnggggttc	caaacccean	ttanntttgg	120
annttaaatt	aaatnttntt	tgnggggnna	anccnaatgt	nangaaagtt	naaccanta	180
tnancttnaa	tnoctggaaa	ccngtngntt	ccaaaaatnt	ttaaccctta	antccctecg	240
aaatngttna	nggaaaaccc	aantttctnt	aaggttggtt	gaaggntnaa	tnaaaanccc	300
nnccaattgt	tttnggccac	gcctgaatta	attggnttcc	gntgttttcc	nttaaaaana	360
ggnnancccc	ggttantnaa	tccccccnnc	cccaattata	ccganttttt	ttngaattgg	420
gancccnccg	gaattaacgg	ggnnnntccc	tnttgggggg	cnggnncccc	ccccntcggg	480
ggttngggnc	aggnchnaat	tgtttaaggg	tccgaaaaat	ccctccnaga	aaaaaanctc	540
ccaggttgag	nntnggggtt	nncccccccc	cangggccct	ctcganaggt	tgggggttgg	600
ggggcctggg	attttntttc	ccctnttnc	tcccccccc	ccnggganag	aggttngngt	660
tttgntcnnc	ggcccnccn	aaganctttn	ccganttnan	ttaaattcct	gcctnggcga	720
agtccnttgn	agggntaaan	ggccccctnn	cggt			754

<210> 21

<211> 755

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(755)

<223> n = A, T, C or G

<400> 21

atcancccat	gacccnaac	nngggacnc	tcanceggnc	nnncnaccnc	cgcccnatca	60
nngtagnnnc	actncnnttn	natcacnccc	cncnactac	gcccnananc	cnacgcncta	120
nncanatncc	actganngcg	cgangtngan	ngagaaanct	nataccanag	ncaccanacn	180
ccagctgtcc	nanaangcct	nnnatacngg	nnnatccaat	ntgnancctc	cnaagtattn	240
nncnncanac	gattttcctn	anccgattac	ccntncccc	tanccctcc	cccccaacna	300
cgaaggcnct	ggncnnaagg	nngcgnccc	ccgctagntc	cccnnaagt	cncnnccta	360
aactcanccn	nattacncgc	ttcntgagta	tcactccccg	aatctcacc	tactcaactc	420
aaaaanacn	gatacaaaa	aatncaagcc	tgnttatnac	actntgactg	ggtctctatt	480
ttagnngtcc	ntnaancntc	ctaatacttc	cagctcncct	tonccaattt	ccnaanggct	540
ctttcngaca	gcatnttttg	gttcccnntt	gggttcttan	ngaattgccc	ttcntngaac	600
gggtctntct	tttccttcgg	ttancctggg	ttcnccggc	cagttattat	ttcccntttt	660
aaattcntnc	cntttanttt	tggcnttcna	aacccccggc	cttgaaaacg	gccccctggg	720
aaaagggttg	tttganaaaa	ttttgtttt	gttcc			755

<210> 22

<211> 849

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(849)
 <223> n = A,T,C or G

<400> 22
 tttttttttt ttttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt 60
 acgctnngan taangcgacc cgantttctag ganncnccct aaaatcanac tgtgaagatn 120
 atcctgnnna cgggaanggtc accggnngat nntgctaggg tgnccnctcc cannncttn 180
 cataactcng nggcctgcc caccaccttc ggcgggccng ngncggggcc cgggtcattn 240
 gnnttaaccn cactnngcna ncggtttccn nccccnncng acccnggcga tccgggggtnc 300
 tctgtcttcc cctgnagncn anaaantggg ccnecggnecc ctttaccctt nnacaagcca 360
 cngcenteta nccnengccc cccctccant nngggggact gccnannigt ccgttntctng 420
 nnaccccnnn gggtncctcg gttgtcgant cnaccgnang ccanggatc cnaaggaagg 480
 tgcgttpttg gcccctaccc ttgcctnccg nncaccttc ccgacnanga nccgtcccg 540
 cncnncgnga cctcncctcg caacaccgc nctctcngt nccggnnccc ccccaccgc 600
 nccctcncnc ngncgnancn ctcnccncc gtctcannca ccaccccgcc ccgccaggcc 660
 ntcanccacn ggnngacnng nagnccntc gcnccgcgcn gdgncnccct cgcncngaa 720
 ctncntcngg ccantnncgc tcaanccnna cnaaacgcg ctgcgcggcc cgnagcgnc 780
 nctcncnca gtcctcccgn cttccnacc angnnttccn cgaggacacn nnaccccgcc 840
 nncangcgg 849

<210> 23
 <211> 872
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(872)
 <223> n = A,T,C or G

<400> 23
 gcgcaaacta tacttcgctc gnactcgtgc gcctcgtcnc tcttttctc cgcaaccatg 60
 tctgacnanc ccgattnggc ngatatcnan aagntcganc agtccaaact gantaacaca 120
 cacacnncan aganaaatcc nctgccttcc anagtanaen attgaacnng agaaccangc 180
 nggcgaatcg taatnaggcg tgcgcgcga atntgtcncc gtttatntn ccagcntcnc 240
 ctncnacc cactctctn nagctgtcnn acccctngtn cgnacccccc naggtcggga 300
 tcgggtttnn nntgaccgng cnnccctcc cccctccat nacganccnc ccgcaccacc 360
 nanngcncgc nccccgmct cttgcgcnc ctgtcctntn cccctgtngc ctggcnengn 420
 accgcattga cctcgcenn ctncnngaaa ncgnanacgt ccgggttggn annancgtg 480
 tgggnnngcg tctgcncgc gttccttcn ncnnetcca ccatcttont tacngggtct 540
 ccncgcctc tcnnncacnc cctgggacgc tntcctntgc ccccttnac tccccctt 600
 cgnctgncc cgncccccacc ntcatttnca nacgntcttc acaannncc ggntnnctcc 660
 cnancngnch gtcanccnag ggaagggng gggnccnntg nttgacgttg ngngangtc 720
 cgaanantcc tcncntcan cnetaccct cgggcgnnt ctengttnc aacttancaa 780
 ntctcccccg ngngcnctc tcagcctcnc cnccecnct ctctgcantg tntctgctc 840
 tnaccnntac gantnttcgn cncctcttt cc 872

<210> 24
 <211> 815
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(815)
 <223> n = A,T,C or G

<400> 24

gcatgcaagc	ttgagtattc	tatagngtca	cctaaatanc	ttggcntaat	catggctcnta	60
nctgncttcc	tgtgtcaaat	gtatacnaaa	tanatatgaa	tctnatntga	caagannngta	120
tctntcatta	gtaacaantg	tnntgtccat	cctgtcngan	canattccca	tnnattncgn	180
cgcattcncn	gncantatn	taatngggaa	ntcnntnnnn	ncaccnncat	ctatcntncc	240
gcncctgac	tggnagagat	ggatnanttc	tnntntgacc	nacatgttca	tcttggattn	300
aananccccc	cgcngnccac	cgggtngnng	cnagccnntc	ccaagacctc	ctgtggaggt	360
aacctgcgtc	aganncatca	aacntgggaa	acccgcnncc	angtnnaagt	ngnnncanan	420
gatcccgtcc	aggnttnacc	atcccttcnc	agcgcacctc	ttngtgcctt	anagnnagc	480
gtgtccnanc	cnetcaacat	ganacgcgcc	agnccanccg	caattnggca	caatgtcgnc	540
gaacccctta	gggggantna	tncaaanccc	caggattgtc	cncncangaa	atccncanc	600
ccnccctac	ccnctttgg	gacngtgacc	aantcccgga	gtncaggtcc	ggcngnctc	660
ccccaccggt	nnccntgggg	gggtgaanct	cngnntcanc	cngncgaggn	ntcgnaagga	720
accggnccctn	ggncgaanng	ancnntcnga	agncccnctn	cgtataaccc	cccctcncca	780
nccnactngnt	agntccccc	cngggtnccg	aangg			815

<210> 25

<211> 775

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(775)

<223> n = A,T,C or G

<400> 25

ccgagatgtc	tcgctccgtg	gccttagctg	tgctcgcgct	actctctctt	tctggcctgg	60
aggctatcca	gcgtactcca	aagattcagg	tttactcacg	tcattccagca	gagaatggaa	120
agtcaaattt	cctgaattgc	tatgtgtctg	ggtttcatcc	atccgacatt	gaanttact	180
tactgaagaa	tgganagaga	attgaaaaag	tgagcattc	agacttgtct	ttcagcaagg	240
actggtcttt	ctatctcntg	tactacactg	aattcacccc	cactgaaaaa	gatgagtatg	300
cctgccgtgt	gaaccatgtg	actttgtcac	agcccaagat	agttaagtgg	gatcgagaca	360
tgtaagcagn	cnnatggaa	gtttgaagat	gccgcatttg	gattggatga	attccaaatt	420
ctgcttgctt	gcnttttaat	antgatatgc	ntatacacc	taccctttat	gncccaaat	480
tgtaggggtt	acatnantgt	tcnctntngg	catgatcttc	ctttataant	ccnccnttcg	540
aattgccgtg	cncnngttn	ngaattgttc	cnnaaccaag	gttggtctcc	ccaggtcncc	600
tcttacggaa	gggcctgggc	cncctttncaa	gggtggggga	accnaaaatt	tcncttntgc	660
ccncccncca	cnntcttgng	nnncantttt	ggaacccttc	cnattccctt	tggcctcnna	720
nccttnncta	anaaaaactn	aaancgtngc	naaanntttt	acttcccccc	ttacc	775

<210> 26

<211> 820

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(820)

<223> n = A,T,C or G

<400> 26

anattantac	agtgtaatct	tttcccagag	gtgtgtanag	ggaacggggc	ctagaggcat	60
cccanagata	ncttatanca	acagtgcctt	gaccaagagc	tgctgggcac	atttcctgca	120
gaaaagggtg	cgtcccccat	cactctctct	ctcccatagc	catcccagag	gggtgagtag	180
ccatcangcc	ttcggtggga	gggagtcang	gaaacaacan	accacagagc	anacagacca	240
ntgatgacca	tgggcggggg	cgagcctctt	ccctgnaccg	gggtggcana	nganagccta	300
nctgaggggt	cacactataa	acgttaacga	ccnagatnan	cacctgcttc	aagtgcaccc	360

ttcctacctg	acnaccagng	accnnnaact	gcngcctggg	gacagcncctg	ggancagcta	420
acnnagcaact	cacctgcccc	cccatggccg	tnccgntccc	tggtcctgnc	aagggaagct	480
ccctgttgga	attncgggga	naccaaggga	nccccctcct	ccanctgtga	aggaaaaann	540
gatggaattt	tncccttccg	gccnntcccc	tcttccttta	cacgccccct	ntactcctc	600
tcctctnttt	ntcctgncnc	acttttnacc	ccnnnatttc	ccttnattga	tcggannctn	660
ganattccac	tnnccgctnc	cntcnatcng	naanacnaaa	nactntctna	cccnggggat	720
gggnncctcg	ntcatcctct	ctttttcnc	accnccnntt	ctttgcctct	ccttngatca	780
tcacaacntc	gntggccntn	ccccccnnn	tcctttncce			820

<210> 27

<211> 818

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(818)

<223> n = A,T,C or G

<400> 27

tctgggtgat	ggcctcttcc	tcctcaggga	cctctgactg	ctctgggcca	aagaatctct	60
tggttcttct	ccgagcccca	ggcagcggtg	attcagccct	gcccacactg	attctgatga	120
ctgcggatgc	tgtgacggac	ccaaggggca	aatagggtcc	cagggtccag	ggagggggcg	180
ctgctgagca	cttcgcgcgc	tcacctgcc	cagccctgc	catgagctct	gggctgggtc	240
tcgcctcca	gggttctgct	cttcangca	ngccancaa	tggcgctggg	ccacactggc	300
ttcttctgct	ccctccctg	gctctgantc	tctgtcttcc	tgctctgtgc	angcnccttg	360
gatctcagtt	tcctctcctc	anngaactct	gtttctgann	tcttcantta	actntgantt	420
tatnaccnan	tggnctgtnc	tgtcnnactt	taatgggccc	gaccggctaa	tcctccctc	480
ntcccttcc	anttcnnna	accngcttnc	cctntcttcc	ccntancecg	ccnggggaanc	540
ctcctttgcc	ctnaccangg	gccnnnaccg	ccctnnctn	ggggggcngg	gtnnctncnc	600
ctgntnnccc	cctcncnnt	tnccctgtcc	cnnccnccgn	nngcannttc	ncngtcccn	660
tnnctcttcn	ngntcgnaa	ngntcncntn	tnnnngncn	ngntnntncn	tcctctcnc	720
cnnntgnang	tnnttnnnnc	ncngnncccc	nnnnccnnnn	nggnantnnn	tctncncngc	780
cccncccc	ngnattaagg	cctccnntct	ccggccnc			818

<210> 28

<211> 731

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(731)

<223> n = A,T,C or G

<400> 28

aggaaggcg	gaggatatt	gtangggatt	gagggatagg	agnataangg	gggaggtgtg	60
tcccaacatg	anggtgngt	tctcttttga	angagggttg	ngtttttann	ccnggtgggt	120
gattnaaccc	cattgtatgg	agnnaaagg	tttnagggat	ttttcggtc	ttatcagtat	180
ntanattcct	gtnaatcgga	aatnatntt	tcnncnggaa	aatnttgctc	ccatccgnaa	240
attntcccc	ggtagtgc	nttnggggg	cngccangtt	tcccaggctg	ctanaatcgt	300
actaaagntt	naagtgggan	tncaaatgaa	aacctnnac	agagnatccn	taccgcactg	360
tnnnntnct	tcgcctntg	actctgcng	agcccaatac	ccnngngnat	gtcncncng	420
nnngcgnenc	tgaaannnnc	tcngggctnn	gancatcang	gggtttcgca	tcaaaagcnn	480
cgtttcncat	naaggcactt	tnccctcatc	caaccnctng	ccctcnncca	tttngccgtc	540
nggttncnct	acgctnnntg	cncctnnntn	ganattttnc	ccgcctnggg	naancctcct	600
gnaatgggta	gggctttntc	ttttnacnnc	ngggntnact	aatcnnctnc	acgctntnctt	660
tctcnacccc	ccccctttt	caatccccanc	ggcnaatggg	gtctccccnn	cgangggggg	720

nnncccannc c

731

<210> 29
 <211> 822
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (822)
 <223> n = A, T, C or G

<400> 29
 actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat 60
 cgctcamacc tcacancctc ccnacnange ctataangaa nannaataga nctgtncnnt 120
 atntntacnc tcatannctt cnnnaccac tccctcttaa cccntactgt gcctatngcn 180
 tnntantct ntgcgcgctn cnanccacon gtggggcnac cncnngnatt ctcnatctcc 240
 tcnccatntn gcctananta ngtncatacc ctatacctac nccaatgcta nnnctaancn 300
 tccatnantt annntaacta ccactgacnt ngactttcnc atnanctcct aatttgaatc 360
 tactctgact cccacngcct annnattagc ancntccccc nachatntct caaccaaadc 420
 ntcaacaacc tatctantctg ttcnccaacc nttnccctcg atccccnnac aacccccctc 480
 ccaaataccc nccacctgac ncctaaccen caccatcccg gcaagccnan ggnccatttan 540
 ccactggaat cacnatngga naaaaaaac ccnaactctc tancncnnat ctccctaana 600
 aatnctcctn naatttactn ncantnccat caanccacn tgaaacnnaa cccctgtttt 660
 tanatccctt ctttcgaaaa ccnacccttt annncccaac ctttngggcc ccccnctcnc 720
 ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaaggcna anannntccg 780
 canatcctat cccttanttn ggggnccctt nccnngggcc cc 822

<210> 30
 <211> 787
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1) ... (787)
 <223> n = A, T, C or G

<400> 30
 cggccgcctg ctctggcaca tgcctcctga atggcatcaa aagtgatgga ctgccattg 60
 ctagagaaga cttctctctc tactgtcatt atggagccct gcagactgag ggctcccctt 120
 gtctgcagga tttgatgtct gaagtctgtg agtgtggctt ggagctcctc atctacatna 180
 gctggaagcc ctggagggcc tctctcgcca gcctccccct tctctccacg ctctccangg 240
 acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga 300
 cccatggggc ctgnaaggcc aggtctcct ttgacacccat ctctcccgct ctgcctggca 360
 ggccgtggga tccactantt ctanaacggg cgccaccnec gtgggagctc cagcttttgt 420
 tcccnttaat gaaggttaat tgcncgcttg gcgtaatcat nggtcanaac tntttcctgt 480
 gtgaaattgt ttntccccctc ncnattccnc ncnacatacn aaccgggaan cataaagtgt 540
 taaagcctgg gggtngecctn nngaanaaac tnaactcaat taattgcgtt ggctcatggc 600
 ccgcttttccn ttcnngaaaa ctgtcntccc ctgcnttntt gaatcgggca ccccnnggg 660
 aaaagcggtt tgcnttttng ggggntcctt ccncttcccc cctcnctaan ccctnccgct 720
 cggtcgttnc nggtngcggg gaangggnat nnnctccenc naagggggng agnnngntat 780
 ccccaaa 822

<210> 31
 <211> 799
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(799)
 <223> n = A,T,C or G

<400> 31

tttttttttt	tttttttggc	gatgctactg	tttaattgca	ggaggtgggg	gtgtgtgtac	60
catgtaccag	ggctattaga	agcaagaagg	aaggagggag	ggcagagcgc	cctgctgagc	120
aacaaaggac	tcctgcagcc	ttctctgtct	gtctcttggc	gcaggcacat	ggggaggcct	180
cccgcagggg	ggggggccacc	agtccagggg	tgggagcact	acanggggtg	ggagtgggtg	240
gtggctggtn	cnaatggcct	gncacanatc	cctacgattc	ttgacacctg	gatttcacca	300
ggggaccttc	tgttctccca	nggnaacttc	ntnnatctcn	aaagaacaca	actgtttctt	360
cngcanttct	ggctgttcat	ggaaagcaca	ggtgtccnat	ttnggctggg	acttgggtaca	420
tatgggtccg	gcccacctct	cccntcnaaa	aagtaattca	cccccccccn	ccntctnttg	480
cctgggcccct	taantaccca	caccggaact	canttannta	ttcatcttng	gntgggcttg	540
ntnatcnccn	cetgaangcg	ccaagtgtga	aggccacgcc	gthcccnctc	cccatagnan	600
nttttntcnt	canctaatac	ccccccnggc	aacnatccaa	tcccccccn	tgggggcccc	660
agcccanggc	ccccgncctg	ggnnnccngn	cncgnantcc	ccaggntctc	ccantcngnc	720
ccnnngcncc	cccgcacgca	gaacanaagg	ntngagccnc	cgcannnnnn	nggtnnccnac	780
ctcgcceccc	ccnnccgngg					799

<210> 32
 <211> 789
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(789)
 <223> n = A,T,C or G

<400> 32

tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tttttccnag	ggcagggtta	ttgacaacct	cncgggacac	aancaggctg	gggacaggac	120
ggcaacaggc	tccggcggcg	gcggcggcgg	ccctacctgc	ggtaccaaata	ntgcagcctc	180
cgctcccgcg	tgatnttcct	ctgcagctgc	aggatgcctt	aaaacagggc	ctcgccntn	240
ggtgggcacc	ctgggatttn	aatttccacg	ggcacaatgc	ggtgcganc	cctcaccacc	300
nattaggaat	agtggtnnta	cccnccnccg	ttggcncact	ccccntggaa	accacttntc	360
gcggotccgg	catctggtct	taaaccttgc	aaacnctggg	gocctctttt	tggttantnt	420
ncnngccaca	atcatnactc	agactggcnc	gggctggccc	caaaaaancn	ccccaaaacc	480
ggnccatgtc	ttnnccgggt	tgctgcnatn	tncatcacct	cccgggcnca	ncaggncaac	540
ccaaaagtgc	ttgngggccn	caaaaaanct	ccggggggnc	ccagtttcaa	caaagtcac	600
ccccttggcc	cccaaatcct	ccccccgntt	netgggtttg	ggaacccacg	cctctnnctt	660
tggngggcaa	gntggntccc	ccttcgggce	cccgggtggc	ccnctcttaa	ngaaaacncc	720
ntcctnnnca	ccatcccccc	nngnnacgnc	tancaangna	tccctttttt	tanaaacggg	780
ccccccnccg						789

<210> 33
 <211> 793
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(793)
 <223> n = A,T,C or G

<400> 33

gacagaacat	gttggatggt	ggagcacctt	tctatacgac	ttacaggaca	gcagatgggg	60
aattcatggc	tgttggagca	atanaacccc	agttctacga	gctgctgatc	aaaggacttg	120
gactaaagtc	tgatgaactt	cccaatcaga	tgagcatgga	tgattggcca	gaaatgaana	180
agaagtttgc	agatgtattt	gcaaagaaga	cgaaggcaga	gtggtgtcaa	atctttgacg	240
gcacagatgc	ctgtgtgact	ccggttctga	cttttgagga	ggttgttcat	catgatcaca	300
acaangaacg	gggctcgttt	atcaccantg	aggagcagga	cgtgagcccc	cgccctgcac	360
ctctgctgtt	aaacacccca	gccatccctt	ctttcaaaaag	ggatccacta	cttctagagc	420
ggnccgccacc	gcggtggagc	tccagotttt	gttcccttta	gtgagggtta	attgcgcgct	480
tggcgtaatc	atggtcatan	ctgttttctg	tgtgaaattg	ttatccgctc	acaattccac	540
acaacatacg	anccggaagc	atnaaatttt	aaagcctggn	ggtngcctaa	tgantgaact	600
nactcacatt	aattggcttt	gcgctcactg	cccgctttcc	agtccggaaa	acctgtcctt	660
gccagctgcc	nttaatgaat	cnggccaccc	cccggggaaa	aggcngtttg	cttnttgggg	720
cgcncctccc	gctttctcgc	ttcctgaant	ccttcccccc	ggtctttcgg	cttgcggcna	780
acggtatcna	cct					793

<210> 34

<211> 756

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(756)

<223> n = A,T,C or G

<400> 34

gccgcgaccg	gcatgtacga	gcaactcaag	ggcgagtggg	accgtaaaaag	ccccaatctt	60
ancaagtgcg	gggaanagct	gggtcgactc	aagctagttc	ttctggagct	caacttcttg	120
ccaaccacag	ggaccaagct	gaccaaacag	cagctaattc	tgccccgtga	catactggag	180
atcgggggccc	aatggagcat	cctacgcaan	gacatccctt	ccttcgagcg	ctacatggcc	240
cagctcaaat	gctactactt	tgattacaan	gagcagctcc	ccgagtcagc	ctatatgcac	300
cagctcttgg	gcctcaacct	cctcttctctg	ctgtcccaga	accgggtggc	tgantnccac	360
acgganttgg	ancggctgcc	tgcccaanga	catacanacc	aatgtctaca	tcnaccacca	420
gtgtccttga	gcaatactga	tgganggcag	ctaccncaaa	gtnttccttg	ccnagggtaa	480
catccccgcg	cgagagctac	accttcttca	ttgacatcct	gctcgacact	atcaggggatg	540
aaaatcgcn	ggttgcctca	gaaaggctnc	aanaanatcc	ttttcnctga	aggcccccg	600
atncnctag	nctagaatcg	gcccgccatc	gcggtgganc	ctccaacctt	tcgttnccct	660
ttactgaggg	ttnattgccg	cccttggcgt	tatcatggtc	acnccngttn	cctgtgttga	720
aattnttaac	ccccacaaat	tccacgccna	cattng			756

<210> 35

<211> 834

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(834)

<223> n = A,T,C or G

<400> 35

ggggatctct	anactnacct	gnatgcatgg	ttgtcggtgt	ggtcgctgtc	gatgaanatg	60
aacaggatct	tgcccttgaa	gctctcggtc	gctgtnttta	agttgctcag	tctgccgtca	120
tagtcagaca	cncctctggg	caaaaaacan	caggatntga	gtcttgattt	cacctccaat	180
aatcttcnng	gctgtctgct	cggtgaactc	gatgacnang	ggcagctggg	tgtgtntgat	240
aaantccanc	angttctcct	tggtgacctc	cccttcaaa	ttgttcgggc	cttcatcaaa	300
cttctnnaan	angannancc	canctttgtc	gagctggnat	ttgganaaca	cgctactgtt	360

ggaaactgat	cccaaaggt	atgtcatcca	tcgcctctgc	tgccctgcaa	aaacttgctt	420
ggcncaaatc	cgactcccn	tccttgaaag	aagccnatca	cacccccctc	cctggactcc	480
nncaangact	ctnccgctnc	ccntccnng	cagggttgg	ggcannccgg	gccentgcgc	540
ttcttcagcc	agttcacnat	nttcacagc	ccctctgcca	gctgtntat	tccttggggg	600
ggaanccgtc	tctcccttcc	tgaannaact	ttgaccgtng	gaatagccgc	gentcnccnt	660
acntnctggg	ccgggttcaa	antccctccn	ttgncnntcn	cctcggggcca	ttctggattt	720
nccnaacttt	ttccttcccc	cnccccncgg	ngtttggnnt	tttcatnggg	ccccaactct	780
gctnttgccc	antcccttgg	gggcntntan	cnccccctnt	ggteccntng	ggcc	834

<210> 36

<211> 814

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(814)

<223> n = A,T,C or G

<400> 36

cggnccgttt	ccngccgcgc	cccgtttcca	tgacnaaggc	tccttccang	ttaaatacnn	60
cctagnaaac	attaatgggt	tgctctacta	atacatcata	cnaaccagta	agcctgcccc	120
naacgccaac	tcaggccatt	cctaccaaag	gaagaaaggc	tggtctctcc	accccctgta	180
ggaaaggcct	gccttgtaag	acaccacaat	ncggctgaat	ctnaagtctt	gtgttttact	240
aatggaaaaa	aaaaataaac	aanagggttt	gttctcatgg	ctgcccaccg	cagcctggca	300
ctaaaacanc	ccagcgctca	cttctgcttg	ganaaatatt	ctttgctctt	ttggacatca	360
ggcttgatgg	tatcaactgc	acntttccac	ccagctgggc	ncccttcccc	catntttgtc	420
antganctgg	aaggcctgaa	nottagtctc	caaaagtctc	ngcccacaag	accggccacc	480
aggggagntc	ntttncagtg	gatctgccaa	anantaccn	tatcatcnnt	gaataaaaag	540
gccccgaac	ganatgcttc	cancancctt	taagaccat	aatcctngaa	ccatgggtgcc	600
cttcgggtct	gatccnaaag	gaatgttcc	gggtcccant	ccctcctttg	tttcttacgt	660
tgtnttgac	ccntgctngn	atnaccaan	tganatcccc	ngaagcacc	tnccctggc	720
atttganttt	cntaaattct	ctgcctacn	nctgaaagca	cnattccctn	ggcnccnaan	780
ggngaactca	agaaggctcn	ngaaaaacca	cncn			814

<210> 37

<211> 760

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(760)

<223> n = A,T,C or G

<400> 37

gcatgctgct	cttcctcaaa	gttggtcttg	ttgccataac	aaccaccata	ggtaaagcgg	60
gogcagtgtt	cgctgaagg	gttgtagtac	cagcgcgagg	tgctctcctt	gcagagtect	120
gtgtctggca	ggctcaacgc	atgccctttg	tcactgggga	aatggatgcg	ctggagctcg	180
tcnaanccac	tcgtgtattt	ttcacangca	gcctcctccg	aagcntccgg	gcagttgggg	240
gtgtcgtcac	actccactaa	actgtcgatn	cancagccca	ttgctgcagc	ggaactgggt	300
gggctgacag	gtgccagaac	acactggatn	ggcctttcca	tggaagggcc	tgggggaaat	360
cncctnancc	caaactgcct	ctcaaaggcc	accttgca	ccccgacagg	ctagaaatgc	420
actcttcttc	ccaaaggtag	ttgttcttgt	tgcccaagca	ncctccanca	aacaaaaanc	480
ttgcaaaatc	tgctccgtgg	gggtcatnnn	taccanggtt	ggggaaaana	acccggcngn	540
ganccnccct	gtttgaatgc	naaggnaata	atcctcctgt	cttgcttggg	tggaaanagca	600
caattgaact	ggttaacntt	ggccgngttc	cncnnggtg	gtctgaaact	aatcacgcgc	660
actggaaaaa	ggtangtgcc	ttccttgaat	tcccaaantt	cccctngntt	tgggtntttt	720

ctectctncc ctaaaaatcg tnttcccccc cntanggcg

760

<210> 38
 <211> 724
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1)...(724)
 <223> n = A, T, C or G

<400> 38
 tttttttttt tttttttttt tttttttttt ttttttaaaaa cccctccat tgaatgaaaa 60
 cttccnfaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc 120
 caaattaatt ttgganttta aattaaatnt tnatnngggg aanaanccaa atgtnaagaa 180
 aatttaaccc attatnaact taaatnccctn gaaacccttg gnttccaaaa atttttaacc 240
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaagggt 300
 ngattttaaac ccccttnant tnttttnacc cnnngctnaa ntatttngnt tccggtgttt 360
 tcctnttaan cntnggtaac tcccgntaat gaannnccct aanccaatta aaccgaattt 420
 tttttgaatt ggaaattccn ngggaattna ccgggggtttt tcccnttttg gggccatncc 480
 ccncttttcg ggggtttgggn ntagggttgaa tttttnnang nccccaaaaa ncccccaana 540
 aaaaaactcc caagnnttaa ttngaantnc ccccttccca ggcctttttg gaaaggnggg 600
 tttntggggg ccngggantt cnttccccn ttncncccc cccccnggt aaanggttat 660
 ngnttttggg ttttgggccc cttnanggac cttccggatn gaaattaaat ccccggnccg 720
 gccg 724

<210> 39
 <211> 751
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(751)
 <223> n = A, T, C or G

<400> 39
 tttttttttt tttttctttg ctcacattta atttttattt tgattttttt taatgctgca 60
 caacacaata tttatttcat ttgtttcttt tatttcatth tatttgtttg ctgctgctgt 120
 tttatttatt tttactgaaa gtgagaggga acttttgttg ccttttttcc tttttctgta 180
 ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aaggggggtt 240
 cgcaaaatca ctcgggggaa nggaaagggt gctttgttaa tcatgcccta tgggtgggtga 300
 ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc ttttaattana 360
 cttgggggtt ccctcccan accaaccnna ctgacaaaaa gtgcngccc tcaaatnatg 420
 tcccggcnnt cnttgaaaca cacngcngaa ngttctcatt ntcccncnc caggtnaaaa 480
 tgaagggtta ccatntttta cncacctcc acntggcnnn gcctgaatcc tcnaaaancn 540
 ccctcaancn aatnctnng ccccggtcnc gcntnngtcc cncocgggct ccgggaantn 600
 cccccnga anncnntnnc naacnaaatt ccgaaaatat tccnntcnc tcaattcccc 660
 cnnagactnt cctcnncnan cncaattttc tttntntcac gaacncgnnc cnnaaaatgn 720
 nnnncnctc cncnngtcn naatcnccan c 751

<210> 40
 <211> 753
 <212> DNA
 <213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(753)
 <223> n = A,T,C or G

<400> 40
 gtgggtatttt ctgtaagatc aggtgttccct cctcgtagg tttagaggaa acaccctcat 60
 agatgaaaac ccccccgaga cagcagcact gcaactgcc aagcagccggg gtaggagggg 120
 cgccctatgc acagctgggc ccttgagaca gcagggttc gatgtcaggc tcgatgtcaa 180
 tgggtctggaa gggcggtctg tacctgcgta ggggcacacc gtcaggggccc accaggaact 240
 tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccagggtgatn agcttggggg 300
 cggtcataa cgcgggtggcg tcgtcgtctg gagctggcag ggccctccgc aggaaggcna 360
 ataaaagggtg cgcggggcga ccgttcanc cgcacttctc naanaccatg angttgggct 420
 cnaaccacc accannccgg acttccttga nggaattccc aaatctcttc gntcttgggc 480
 ttctnctgat gccctanctg gttgcccn gnagccaan nccccaancc ccgggggtcct 540
 aaanaccn cctcctcmtt tcatctgggt tntntcccc ggacntgggt tctctcaag 600
 ggancccata tctcnaccan tactcacnt nccccccnt gnnaccanc cttctanngn 660
 ttccncccg nccctctggc cntcaaan gcttnacna cctgggtctg ccttcccccc 720
 tnccctatct gnaccccn tttgtctcan tnt 753

<210> 41
 <211> 341
 <212> DNA
 <213> Homo sapien

<400> 41
 actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaagt 60
 agtgaacca tccttgattt atatacatat atgttctcag tattttggga gcctttccac 120
 ttcttttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt 180
 tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttgag 240
 tggtaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat 300
 ttttactttt tgattaattg tgttttatat attagggtag t 341

<210> 42
 <211> 101
 <212> DNA
 <213> Homo sapien

<400> 42
 acttactgaa tttagttctg tgctcttccct tatttagtgt tgtatcataa atactttgat 60
 gtttcaaaca ttctaaataa ataattttca gtggcttcat a 101

<210> 43
 <211> 305
 <212> DNA
 <213> Homo sapien

<400> 43
 acatctttgt tacagtctaa gatgtgttct taaatcacca ttccttctctg gtcctcaccc 60
 tccagggtgg tctcacactg taattagagc tattgaggag tctttacagc aaattaagat 120
 tcagatgcct tgctaagtct agagttctag agttatgttt cagaaagtct aagaaacca 180
 cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat 240
 tggatacaga acgagagtta tccctggataa ctcagagctg agtacctgcc cggggggccg 300
 tcgaa 305

<210> 44
 <211> 852
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(852)
 <223> n = A,T,C or G

<400> 44
 acataaatat cagagaaaag tagtctttga aatattttacg tccaggagtt ctttgtttct 60
 gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt 120
 ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct 180
 ccagaatttc tctttttag tagtatctca tagctcggct gagcttttca taggtcatgc 240
 tgctgttggt cttcttttta ccccatagct gagccactgc ctctgatttc aagaacctga 300
 agacgccctc agatcggctt tcccatttta ttaatcctgg gttcttgtct gggttcaaga 360
 ggatgtcgcg gatgaattcc cataagttag tccctctcgg gttgtgcttt ttggtgtggc 420
 acttgfcagg ggggtcttgc tcttttttca tatcaggtag ctctgcaaca ggaaggtgac 480
 tgggtggtgt catggagatc tgagcccgge agaaagtatt gctgtccaac aaatctactg 540
 tgctaccata gttggtgtca tataaatagt tctngtcttt ccagggtgtc atgatggaag 600
 gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc 660
 actggccgtt ccacttcaga tgctgcaagt tgctgtagag gagntgcccc gccgtccctg 720
 ccgccgggt gaactcctgc aaactcatgc tgcaaaggtg ctgccggtg atgtcgaact 780
 cntggaaagg gatacaattg gcatccagct ggttggtgtc caggaggtga tggagccact 840
 cccacacctg gt 852

<210> 45
 <211> 234
 <212> DNA
 <213> Homo sapien

<400> 45
 acaacagacc cttgctcgtt aacgacctca tgctcatcaa gttggacgaa tccgtgtccg 60
 agtctgacac catccggagc atcagcattg cttcgcagtg ccctaccgcg gggaaactctt 120
 gcctcgtttc tggctggggg ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg 180
 tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgaccgg ctgt 234

<210> 46
 <211> 590
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(590)
 <223> n = A,T,C or G

<400> 46
 actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta 60
 atttgatagc aatatttttg agattacaga gttttagtaa ttaccaatta cacagttaaa 120
 aagaagataa tatattccaa gcanatacaa aatatctaata gaaagatcaa ggcaggaaaa 180
 tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta 240
 aaagctttca aaanaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat 300
 caggataaan aactgaagg canaaagaat taattttcac ttcattgtaac ncacccanat 360
 ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aagggtctttc 420
 tggctcttaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag 480
 ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct 540
 gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt 590

<210> 47
 <211> 774

<212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(774)
 <223> n = A,T,C or G

<400> 47
 acaagggggc ataatgaagg agtggggana gatttttaaag aaggaaaaaa aacgaggccc 60
 tgaacagaat tttcctgnac aacggggcctt caaaataatt ttcttgggga gggtcaagac 120
 gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg 180
 cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa 240
 aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggtctt 300
 cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctctgtgtg 360
 ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgtgat cctgcgtggc 420
 ccacactcct tgaacacaca tccccaggtt atattcctgg acatggctga acctcctatt 480
 cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctocaaacc 540
 acggcatggg aagcctttct gacttgccctg attactccag catcttggaa caatccctga 600
 ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttgagacc 660
 aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct 720
 tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt 774

<210> 48
 <211> 124
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(124)
 <223> n = A,T,C or G

<400> 48
 canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt 60
 ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact 120
 tggt 124

<210> 49
 <211> 147
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(147)
 <223> n = A,T,C or G

<400> 49
 gccgatgcta ctatttttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt 60
 tgtggctaca ggtgggtgtc gactgcatna aaaanttttt tacgggtgat tgcaaaaatt 120
 ttagggcacc catatcccaa gcantgt 147

<210> 50
 <211> 107
 <212> DNA
 <213> Homo sapien

<400> 50
 acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatatattgc 60
 atggtttgag gttaggagga gttaggcata tgttttggga gaggggt 107

<210> 51
 <211> 204
 <212> DNA
 <213> Homo sapien

<400> 51
 gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgacagg 60
 cggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag 120
 gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgcc cacttgcca 180
 cctccctttt gggaccagca atgt 204

<210> 52
 <211> 491
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(491)
 <223> n = A,T,C or G

<400> 52
 acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaaggtta gtatttgtga 60
 gggatatttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca 120
 ccatcagaca ggttttttaa aaacaacata ttacaaaatt agacaatcat ctttaaaaaa 180
 aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt 240
 tcanaaacac ttctcaaaa attttcaana tggtagcttt canatgtnc ctcagtccca 300
 atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc 360
 atgcaacagt gtcttttctt tnccttttct tttttttttt ttacaggcac agaaactcat 420
 caattttatt tggataacaa aggggtctcca aattatatgt aaaaataaat ccaagttaat 480
 atcactcttg t 491

<210> 53
 <211> 484
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(484)
 <223> n = A,T,C or G

<400> 53
 acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga 60
 gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac 120
 actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct 180
 caatcaaadc tctacataac actatagtaa ttaaaacggt aaaaaaaagt gttgaaatct 240
 gactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc 300
 agctttgant ttctttgtgc tgatangagg aaaggctgaa ttaccttgtt gcctctccct 360
 aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg 420
 tanccttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc 480
 cant 484

<210> 54

<211> 151
 <212> DNA
 <213> Homo sapien

<400> 54
 actaaacctc gtgcttgtga actccataca gaaaacgggtg ccatcootga acacgggtgg 60
 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120
 tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55
 <211> 91
 <212> DNA
 <213> Homo sapien

<400> 55
 acctggcttg tctccgggtg gttcccggtg cccccacgg tccccagaac ggacactttc 60
 gccctccagt ggatactcga gccaaagtgg t 91

<210> 56
 <211> 133
 <212> DNA
 <213> Homo sapien

<400> 56
 ggcggatgtg cggttggttat atacaaatat gtcattttat gtaagggtact tgagtatact 60
 tggatttttg gtatctgtgg gttgggggga cgggccagga accaatacc catggatacc 120
 aagggacaac tgt 133

<210> 57
 <211> 147
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(147)
 <223> n = A,T,C or G

<400> 57
 actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gngtgggcg 60
 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120
 tctcantggg ctggatncat gcagggt 147

<210> 58
 <211> 198
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(198)
 <223> n = A,T,C or G

<400> 58
 acagggatat aggtttnaag ttattgtat tgtaaaatac attgaatttt ctgtatactc 60
 tgattacata catttatact ttaaaaaaga tgtaaatctt aatttttatg ccatctatta 120
 atttaccat gagttacctt gtaaagtaga agtcatgata gcactgaatt ttaactagtt 180
 ttgacttcta agtttggt 198

<210> 59
 <211> 330
 <212> DNA
 <213> Homo sapien

<400> 59
 acaacaaatg ggttgtgagg aagtcttatac agcaaaaactg gtgatggcta ctgaaaagat 60
 ccattgaaaa ttatcattaa tgatttttaa tgacaagtta tcaaaaactc actcaatttt 120
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa 180
 tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagaccag 240
 cagaaggat ctattttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt 300
 tttcgtcttt attggacttc ttgaagagt 330

<210> 60
 <211> 175
 <212> DNA
 <213> Homo sapien

<400> 60
 accgtgggtg ctttctacat tcttgacggc tccttcacca acatctggtt ctacttcggc 60
 gtcgtgggct ctttctctt catctcctc cagctggtgc tgctcatcga ctttgccgac 120
 tcctggaacc agcgtggtg gggcaaggcc gaggagtgcg attcccgtgc ctggt 175

<210> 61
 <211> 154
 <212> DNA
 <213> Homo sapien

<400> 61
 accccacttt tcttctgtg agcagtctgg acttctcact gctacatgat gaggggtgagt 60
 ggtgtgtgct cttcaacagt atctctccct ttccggatct gctgagccgg acagcagtgc 120
 tggactgcac agccccgggg ctccacattg ctgt 154

<210> 62
 <211> 30
 <212> DNA
 <213> Homo sapien

<400> 62
 cgctcgagcc ctatagttag tcgtattaga 30

<210> 63
 <211> 89
 <212> DNA
 <213> Homo sapien

<400> 63
 acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc 60
 ctgtatgaat aaaaatgggt atgtcaagt 89

<210> 64
 <211> 97
 <212> DNA
 <213> Homo sapien

<400> 64
 accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag 60

aatcagtgc tccaggattg gtccttggat ctgggggt

97

<210> 65
 <211> 377
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(377)
 <223> n = A,T,C or G

<400> 65
 acaacaanaa ntcccttctt taggccaactg atggaaacct ggaacccctt tttgatggca 60
 gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntoccaa accgcacacc 120
 ccaaccctgg tctaccaca nttctggcta tgggctgtct ctgccactga acatcagggt 180
 tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa 240
 ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaaccg 300
 tgggggtgaa ctaccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360
 gggcgggagg agcatgt 377

<210> 66
 <211> 305
 <212> DNA
 <213> Homo sapien

<400> 66
 acgcctttcc ctcagaattc agggaagaga ctgtcgctg ccttcctccg ttgttgctg 60
 agaaccctg tgcccttcc caccatatcc accctcgctc catctttgaa ctcaaacag 120
 aggaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tccctcacct 180
 tctccactc taagggatat caacactgcc cagcacagg gccctgaatt tatgtggttt 240
 ttatatattt tttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300
 tggtt 305

<210> 67
 <211> 385
 <212> DNA
 <213> Homo sapien

<400> 67
 actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga 60
 ggtcggacca gccacatctc atgtgcaaga ttgccagca gacatcagg ctgagagttc 120
 cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc 180
 tgtgtgtgctc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg 240
 ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg 300
 cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac 360
 catagtttct gtgctagtgg accgt 385

<210> 68
 <211> 73
 <212> DNA
 <213> Homo sapien

<400> 68
 acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa 60
 gtttttttaa tgg 73

<210> 69

<211> 536
 <212> DNA
 <213> Homo sapien
 <220>
 <221> misc_feature
 <222> (1)...(536)
 <223> n = A,T,C or G

<400> 69
 actagtcag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctctgcagc 60
 tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct 120
 cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat 180
 cccgggtggc atctataagc cagacotcaa tgatgagtgg gtacagcgtg cccttcactt 240
 cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgtgcggtg 300
 actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg 360
 ccgaaccata tgtaccaagt cccagcccaa ctgggacacc tgtgccttcc atgaacagcc 420
 agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca 480
 gaangtcctt gggtgaaatc cagggtgtcaa gaaatcctan ggatctgttg ccaggc 536

<210> 70
 <211> 477
 <212> DNA
 <213> Homo sapien

<400> 70
 atgaccctta acagggggccc tctcagccct cctaatagacc tccggcctag ccatgtgatt 60
 tcacttccac tccataacgc tctcataact aggcctacta accaacacac taaccatata 120
 ccaatgatgg cgcgatgtaa cagagaaaag cacataccaa ggccaccaca caccacctgt 180
 ccaaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc 240
 agggattttt ctgagccttt taccactcca gcctagcccc taccocccaa ctaggagggc 300
 actggccccc aacaggcatc accccgctaa atccoctaga agtcccactc ctaaacacat 360
 ccgtattact cgcacagga gtatcaatca cctgagctca ccatagtcta atagaaaaca 420
 accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt 477

<210> 71
 <211> 533
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(533)
 <223> n = A,T,C or G

<400> 71
 agagctatag gtacagtgtg atctcagctt tgcaaacaca tttctacat agatagtact 60
 aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta 120
 tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat 180
 attattttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt 240
 taaataaagg tttgtcatct ttaaaaatac agcaatatgt gactttttta aaaagctgtc 300
 aaatagggtg gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca 360
 agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg 420
 cttcgttaatt ttggagtang aggttcctc ctcaattttg tattttttaa aagtcacatgg 480
 taaaaaaaaa aattcacaaac agtatataag gctgtaaaat gaagaattct gcc 533

<210> 72
 <211> 511

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 72
tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta 60
aaatgaaagg ottccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa 120
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga 180
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattggt attacanagt 240
gaggttctct gtgtgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca 300
cacatgagaa ctgaaatggc ccaaaccag aaagaaagcc caactagatc ctcagaanac 360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgcccc gtctgttatg 420
atttctctcc attgcagcna naaaccggtt cttctaagca aacncagggtg atgatggcna 480
aaatacacc cctcttgaag naccnggagg a 511

<210> 73
<211> 499
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(499)
<223> n = A,T,C or G

<400> 73
cagtgccagc actgggtgcc gtaccagtac caataacagt gccagtgcc gtgccagcac 60
cagtgggtggc ttcagtgtct gtgccagcct gaccgccact ctcacatttg ggctcttcgc 120
tggccttggg ggagctgggt ccagcaccag tggcagctct ggtgcctgtg gtttctccta 180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc aggggtgcac 240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca 300
ctctgcatta aatctatttg ccatttctga aaaaaaaaaa aaaaaaaggg cggccgctcg 360
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc 420
catctgttgt ttgcccctcc cccgntgcct tccttgacct tggaaagtgc cactccact 480
gtcctttcct aantaaaat 499

<210> 74
<211> 537
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(537)
<223> n = A,T,C or G

<400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat 60
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact 120
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa 180
cattgtatgc atggaaacat ggaggaacag tattacagtg tctaccact ctaatcaaga 240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag 300
ggcctttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc 360
cagtttgctt gatataattt ttgatattaa gattcttgac ttatatattt aatgggttct 420

actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat 480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt 537

<210> 75
<211> 467
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(467)
<223> n = A,T,C or G

<400> 75
caaandcaat tgttcaaaaag atgcaaataa tacactactg ctgcagctca caaacacctc 60
tgcattattac acgtacctcc tctgtctcct caagtagtgt ggtctatatt gccatcatca 120
cctgtctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg 180
tggcacaagg aggccatctt ttctcatcgt gttattgtcc ctagaagcgt cttctgagga 240
tctagttggg ctttctttct ggggttgggc catttcantt ctcatgtgtg tactattcta 300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa 360
caatgaggaa tagccacggg gatctccagc accaaatctc tccatgttnt tccagagctc 420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn 467

<210> 76
<211> 400
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(400)
<223> n = A,T,C or G

<400> 76
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctgcgcgtac 60
tctctctttc tggcctggag gctatccagc gtactccaaa gattcaggtt tactcacgtc 120
atccagcaga gaattgaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat 180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag 240
acttgtcttt cagcaaggac tggctcttct atctcttgta ctacactgaa ttcaccccca 300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng 360
ttnagtggga tctganacatg taagcagcan catgggaggt 400

<210> 77
<211> 248
<212> DNA
<213> Homo sapien

<400> 77
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60
ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggtg tgattgtgc 120
caggcactgt tcatctcagc ttttctgtcc ctttgtctcc ggcaagcgt tctgtgaaa 180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgtctccac ccgaaaaaaa 240
aaaaaaaa 248

<210> 78
<211> 201
<212> DNA
<213> Homo sapien

<400> 78
 actagtccag tgtggtggaa ttccattgtg ttggggcccaa cacaatggct acctttaaca 60
 tcacccagac cccgccctgc ccgtgcccca cgctgctgct aacgacagta tgatgcttac 120
 tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttggtt ataaatgcct 180
 gatttaaaaa aaaaaaaaaa a 201

<210> 79
 <211> 552
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(552)
 <223> n = A,T,C or G

<400> 79
 tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg 60
 tttaggcagt gctagtaatt tctcgtaat gattctgtta ttactttcct attctttatt 120
 cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag 180
 tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt 240
 atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact 300
 ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga 360
 taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta 420
 ttcccaggaa tatgggggtc atttatgaat antaccggg anagaagttt tgantnaaac 480
 cngtttttgt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa 540
 aaaaaaaaaa aa 552

<210> 80
 <211> 476
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(476)
 <223> n = A,T,C or G

<400> 80
 acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga 60
 ggggaaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct 120
 cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt 180
 gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta 240
 aggttaaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac 300
 tctttctaagt cctcttccag cctcactttg agtcctcctt gggggttgat aggaantntc 360
 tcttggtttt ctcaataaaa tctctatoca tctcatgttt aatttggtac gcntaaaaat 420
 gctgaaaaaa ttaaaatggt ctggtttcnc tttaaaaaaa aaaaaaaaaa aaaaaa 476

<210> 81
 <211> 232
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(232)
 <223> n = A,T,C or G

<400> 81

tttttttttg	tatgccntcn	ctgtggngtt	attgttgctg	ccaccctgga	ggagcccagt	60
ttcttctgta	tctttctttt	ctgggggata	ttcttggtc	tgccctcca	ttcccagcct	120
ctcatcccca	tcttgcaact	ttgctagggg	tggaggcgct	ttcttggtag	cccctcagag	180
actcagtcag	cggaataag	tcttaggggt	ggggggtgtg	gcaagccggc	ct	232

<210> 82

<211> 383

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(383)

<223> n = A,T,C or G

<400> 82

aggcgggagc	agaagctaaa	gccaaagccc	aagaagagt	gcagtgccag	cactggtgcc	60
agtaccagta	ccaataacat	gccagtgcc	gtgccagcac	cagtgggtggc	ttcagtgtg	120
gtgccagcct	gaccgccact	ctcacatttg	ggctcttcgc	tggccttggt	ggagctgggt	180
ccagcaccag	tggcagctct	ggtgcctgtg	gtttctccta	caagtggat	tttagatatt	240
gttaatcctg	ccagtctttc	tcttcaagcc	agggtgcata	ctcagaaacc	tactcaacac	300
agcactctng	gcagccacta	tcaatcaatt	gaagttgaca	ctctgcatta	aatctatttg	360
ccatttcaaa	aaaaaaaaaa	aaa				383

<210> 83

<211> 494

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(494)

<223> n = A,T,C or G

<400> 83

accgaattgg	gaccgctggc	ttataagcga	tcatgtcttc	cagtattacc	tcaacgagca	60
gggagatcga	gtctatacgc	tgaagaaatt	tgaccgatg	ggacaacaga	cctgctcagc	120
ccatcctgct	cggttctccc	cagatgacaa	atactctcga	caccgaatca	ccatcaagaa	180
acgcttcaag	gtgctcatga	cccagcaacc	gcgccctgtc	ctctgagggg	ccttaaactg	240
atgtcttttc	tgccacctgt	taccctctcg	agactccgta	accaaactct	tgggactgtg	300
agccctgatg	cctttttgcc	agccatactc	tttggcntcc	agtctctcgt	ggcgattgat	360
tatgcttggtg	tgaggcaatc	atggtggcat	cacccatnaa	gggaacacat	ttganttttt	420
tttncatat	tttaaattac	naccagaata	nttcagaata	aatgaattga	aaaactctta	480
aaaaaaaaaa	aaaa					494

<210> 84

<211> 380

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(380)

<223> n = A,T,C or G

<400> 84

```

gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca      60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag      120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg      180
gcacaccctc ctggggccca ggcgggcacc tgcgtctccc agtatgcaa ctggctggtg      240
gtgctgctcc tgcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg      300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc      360
agcgttncgg cctcatccgg

```

```

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

```

```

<400> 85
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc      60
tnccatcgtc atactgtagg ttggccacca cctcctgcat cttggggcgg ctaatatcca      120
ggaaactctc aatcaagtca ccgctcnatna aacctgtggc tggttctgtc ttccgctcgg      180
tgtgaaagga tctccagaag gagtgcctga tcttccccac acttttcatg actttattga      240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagttag gtcaccagcc      300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggg gnagtctcac      360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggngaa      420
aaagaacacc tcctggaagt gctngccgct cctcgtcent tggtggnngc gentnccttt      480
t

```

```

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt      60
acttgaaaaa gcaacttnaa gcctggacac tggattataa attcacaata tgcaaacatt      120
taaacagtgt gtcaatctgc tcccttaactt tgatcatcacc agtctgggaa taagggtatg      180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga      240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gtagccaat tcactttctt      300
catgggacag agccatttga tttaaaaaagc aaattgcata atattgagct ttgggagctg      360
atatntgagc ggaagantag cctttctact tcaccagaca caactccttt catattggga      420
tgtnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg      472

```

```

<210> 87
<211> 413
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G

```

<400> 87
 agaaaccagt atctctnaaa acaacctctc ataccttggtg gacctaatTT tgtgtgcgtg 60
 tgtgtgtgcg cgcataattat atagacaggc acatcttttt tacttttgta aaagcttatg 120
 cctcttttgt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180
 ttgtcttctg tgtaaattgt actagagaaa acacctatnt tatgagtcaa tctagttngt 240
 tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg 300
 ggggacaaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa 360
 acagaaattg ggtngtatat tgaaanang catcattnaa acgttttttt ttt 413

<210> 88

<211> 448

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(448)

<223> n = A,T,C or G

<400> 88
 cgcagcgggt cctctctatc tagctccagc ctctcgctg ccccaactccc cgcgtcccgc 60
 gtcctagccn accatggcgc ggccctgog cgcctcgctg ctctgctgg ccactcctggc 120
 cgtggccctg gccgtgagcc ccgcggccgc ctccagctcc ggcaagccgc cgcgcctggt 180
 gggaggccca tggacccgc gtggaagaag aagggtgtgc gcgtgcactg gactttgccg 240
 tcggcnanta caacaaaccc gcaacnactt ttaccnagcn cgcgctgcag gttgtgccgc 300
 cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng 360
 tttaccagaa ccnagccaat tngaacaatt nccctccat aacagcccct tttaaaaagg 420
 gaancantcc tgnctctttc caaatttt 448

<210> 89

<211> 463

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(463)

<223> n = A,T,C or G

<400> 89
 gaattttgtg cactggccac tgtgatggaa ccattggggc aggatgcttt gagtttatca 60
 gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc 120
 agagggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt 180
 ctcaagtaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc 240
 tttnatgttn agacttgect ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg 300
 ttttaaaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn 360
 aattctctcc ccatannaaa acccangccc ttggganaat ttgaaaaang gntccttcnn 420
 aattcnnana anttcagntn tcatacaaca naacngganc ccc 463

<210> 90

<211> 400

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(400)

<223> n = A, T, C or G

<400> 90

agggattgaa	ggtctnttnt	actgtcggac	tggtcancca	ccaactctac	aagttgctgt	60
cttccactca	ctgtctgtaa	gcntnttaac	ccagactgta	tcttcataaa	tagaacaat	120
tcttcaccag	tcacatcttc	taggaccttt	ttggattcag	ttagtataag	ctcttcact	180
tcctttgtta	agacttcac	tggtaaagtc	ttaggttttg	tagaaaggaa	tttaattgct	240
cggttctctaa	caatgtcctc	tccttgaagt	atttggctga	acaaccacc	tnaagtcct	300
ttgtgcatcc	attttaaata	tacttaatag	ggcattggtn	cactaggtta	aattctgcaa	360
gagtcactctg	tctgcaaaaag	ttgcgttagt	atatctgcca			400

<210> 91

<211> 480

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(480)

<223> n = A, T, C or G

<400> 91

gagctcggat	ccaataatct	ttgtctgagg	gcagcacaca	tatncagtgc	catggnaact	60
ggtctacccc	acatgggagc	agcatgccgt	agntatataa	ggtcattccc	tgagtcagac	120
atgcctcttt	gactaccgtg	tgccagtgtc	gggtgattctc	acacacctcc	nncgctctt	180
tgtggaaaaa	ctggcacttg	nctggaacta	gcaagacatc	acttacaat	tcacccacga	240
gacacttgaa	aggtgtgaaca	aagcgactct	tgcatgtctt	tttgtccctc	cggcaccagt	300
tgtcaatact	aacccgctgg	tttgctcca	tcacatttgt	gatctgtagc	tctggataca	360
tctcctgaca	gtactgaaga	acttctctt	ttgtttcaaa	agcaactctt	ggtgcctgtt	420
ngatcagggt	cccatttccc	agtcggaatg	ttcacatggc	atatnttact	tcccacaaaa	480

<210> 92

<211> 477

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(477)

<223> n = A, T, C or G

<400> 92

atacagccca	natcccacca	cgaagatgcg	cttggtgact	gagaacctga	tgcggtcact	60
ggtcccgtg	tagccccagc	gactctccac	ctgctggaag	cggttgatgc	tgactcctt	120
cccacgcagg	cagcagcggg	gccggtcaat	gaactccact	cgtggcttgg	ggttgacggt	180
taantgcagg	aagaggctga	ccacctcgcg	gtccaccagg	atgcccgact	gtgcgggacc	240
tgacgcgaaa	ctcctcgatg	gtcatgagcg	ggaagcgaat	gangcccagg	gccttgccca	300
gaaccttcgc	cctgttctct	ggcgtcacct	gcagctgctg	cggctnacac	tcggcctcgg	360
accagcggac	aaacggcggt	gaacagccgc	acctcacgga	tgcccantgt	gtcgcgctcc	420
aggaacggcn	ccagcgtgtc	caggtcaatg	tcggtgaanc	ctccgcgggt	aatggcg	477

<210> 93

<211> 377

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(377)

<223> n = A,T,C or G

<400> 93

gaacggctgg	accttgccctc	gcattgtgct	gctggcagga	ataccttggc	aagcagctcc	60
agtccgagca	gccccagacc	gctgccgccc	gaagctaagc	ctgcctctgg	ccttccccctc	120
cgcctcaatg	cagaaccant	agtgggagca	ctgtgttttag	agttaagagt	gaacactgtg	180
tgattttact	tggaatttc	ctctgttata	tagcttttcc	caatgcta	ttccaaacaa	240
caacaacaaa	ataacatgtt	tgctgttna	gttgataaaa	agtangtgat	tctgtatnta	300
aagaaaatat	tactgttaca	tatactgctt	gcaanttctg	tattttattgg	tnctctggaa	360
ataaatatat	tattaaa					377

<210> 94

<211> 495

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(495)

<223> n = A,T,C or G

<400> 94

ccctttgagg	ggtagggctc	cagttcccag	tggaagaaac	aggccaggag	aantgcgtgc	60
cgagctgang	cagatttccc	acagtgaacc	cagagccctg	ggctatagtc	tctgaccctt	120
ccaaggaaa	accaccttct	ggggacatgg	gctggagggc	aggacctaga	ggcaccaagg	180
gaaggcccca	ttccggggct	gttccccgag	gaggaaggga	aggggctctg	tgtgccccc	240
acgaggaana	ggcctgtant	cctgggatca	nacaccctt	cacgtgtatc	cccacacaaa	300
tgcaagctca	ccaaggtccc	ctctcagtc	cttccctaca	ccctgaacgg	ncactggccc	360
acaccacccc	agancancca	cccgccatgg	ggaatgtnt	caaggaatcg	cngggcaacg	420
tggactctng	tcccnnaagg	gggcagaatc	tccaatagan	gganngaacc	cttgctnana	480
aaaaaaaaana	aaaaa					495

<210> 95

<211> 472

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(472)

<223> n = A,T,C or G

<400> 95

ggttacttgg	tttcattgcc	accacttagt	ggatgtcatt	tagaaccatt	ttgtctgctc	60
cctctggaag	ccttgcgag	agcggacttt	gtaattgttg	gagaataact	gctgaatttt	120
tagctgtttt	gagttgattc	gcaccactgc	accacaactc	aatatgaaaa	ctatttnact	180
tatttattat	cttgtgaaaa	gtatacaatg	aaaattttgt	tcatactgta	tttatcaagt	240
atgatgaaaa	gcaatagata	tatattcttt	tattatgttn	aattatgatt	gccattatta	300
atcggaacaaa	tgtggagtgt	atgttctttt	cacagtaata	tatgcctttt	gtaacttcac	360
ttggttattt	tattgtaaat	gaattacaaa	attcttaatt	taagaaaatg	gtangttata	420
tttanttcan	taatttcttt	ccttgtttac	gttaattttg	aaaagaatgc	at	472

<210> 96

<211> 476

<212> DNA

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(476)
 <223> n = A,T,C or G

<400> 96
 ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat 60
 gtgggtgaaat ttcaaaatta tatgtaactt ctactagttt tacttttctcc cccaagtctt 120
 ttttaactca tgattttttac acacacaatc cagaacttat tatatagcct ctaagtcttt 180
 attcttcaca gtagatgatg aaagagtcct ccagtgtctt gngcanaatg ttctagntat 240
 agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat 300
 tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct 360
 gcaggtaact ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt 420
 taaaaagtct atcttcctca nangtctgtt aaggaacaat ttaatcttct agcttt 476

<210> 97
 <211> 479
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(479)
 <223> n = A,T,C or G

<400> 97
 actcttttcta atgctgatat gatcttgagt ataagaatgc atatgtcact agaattggata 60
 aaataatgct gcaaaacttaa tgttctttatg caaaatggaa cgctaatagaa acacagctta 120
 caatcgcaaa tcaaaaactca caagtgtctca tctgttgtag atttagtgta ataagactta 180
 gattgtgctc cttooggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat 240
 caggctacta gaattctggt attggatatn tgagagcatg aaatttttaa naatacactt 300
 gtgattatna aattaatcac aaatttctact tatacctgct atcagcagct agaaaaacat 360
 ntnnttttta natcaaagta ttttgtgttt ggaantgttn aaatgaaatc tgaatgtggg 420
 ttcnatctta ttttttcccn gacnactant tnccttttta gggncctattc tganccatc 479

<210> 98
 <211> 461
 <212> DNA
 <213> Homo sapien

<400> 98
 agtgacttgt cctccaacaa aacccttga tcaagtttgh ggcaactgaca atcagaccta 60
 tgctagttcc tgtcatctat tgcgtactaa atgcagactg gagggggacca aaaaggggca 120
 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240
 tgaagccact ctgaacacgc tggttatcta gatgagaaca gagaaataaa gtcagaaaaat 300
 ttacctggag aaaagaggct ttggctgggg accatcccat tgaaccttct cttaaggact 360
 ttaagaaaaa ctaccacatg ttgtgtatcc tgggtgccggc cgtttatgaa ctgaccaccc 420
 tttggaataa tcttgacgct cctgaacttg ctctctgcg a 461

<210> 99
 <211> 171
 <212> DNA
 <213> Homo sapien

<400> 99
 gtggccgcgc gcaggtgttt cctcgtaacc cagggecccc tcccttcccc aggcgtccct 60
 cggcgectct gcgggcccga ggaggagcgg ctggcggttg gggggagtgt gaccacccct 120

cggtgagaaa agccttctct agcgatctga gaggcgtgcc ttgggggtac c 171

<210> 100
 <211> 269
 <212> DNA
 <213> Homo sapien

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 <212> DNA
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 <211> 470
 <212> DNA
 <213> Homo sapien

<400> 102
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 <211> 581
 <212> DNA
 <213> Homo sapien

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581

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<212> DNA
<213> Homo sapien

<400> 104

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<210> 105
<211> 538
<212> DNA
<213> Homo sapien

<400> 105

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<212> DNA
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<400> 106

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<211> 1621
<212> DNA
<213> Homo sapien

<400> 107

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a 1621

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<210> 108
 <211> 382
 <212> PRT
 <213> Homo sapien

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Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg
          35          40          45
Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala
          50          55          60
Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe
          65          70          75          80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln
          85          90          95
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln
          100          105          110
Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala
          115          120          125
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr
          130          135          140
Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys
          145          150          155          160
Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys
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Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg

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195	200	205
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225	230	235
Tyr Glu Leu Leu Ile Lys Gly Leu Gly Leu Lys Ser Asp Glu Leu Pro		
245	250	255
Asn Gln Met Ser Met Asp Asp Trp Pro Glu Met Lys Lys Lys Phe Ala		
260	265	270
Asp Val Phe Ala Lys Lys Thr Lys Ala Glu Trp Cys Gln Ile Phe Asp		
275	280	285
Gly Thr Asp Ala Cys Val Thr Pro Val Leu Thr Phe Glu Glu Val Val		
290	295	300
His His Asp His Asn Lys Glu Arg Gly Ser Phe Ile Thr Ser Glu Glu		
305	310	315
Gln Asp Val Ser Pro Arg Pro Ala Pro Leu Leu Leu Asn Thr Pro Ala		
325	330	335
Ile Pro Ser Phe Lys Arg Asp Pro Phe Ile Gly Glu His Thr Glu Glu		
340	345	350
Ile Leu Glu Glu Phe Gly Phe Ser Arg Glu Glu Ile Tyr Gln Leu Asn		
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<210> 109

<211> 1524

<212> DNA

<213> Homo sapien

<400> 109

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<210> 110

<211> 3410
 <212> DNA
 <213> Homo sapien

<400> 110

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 <212> DNA
 <213> Homo sapien

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tacaataagt	ccacttctgc	ctctgccact	actgctgccca	catgggaact	gtgaagaggc		900
accctggcaa	gcagcagtg	ttggggggagg	ggacaggatc	taacaatgtc	acttggggcca		960
gaatggacct	gccctttctg	ctccagactt	ggggctagat	agggaccact	ccttttagcg		1020
atgcctgact	ttccttccat	tggtgggtgg	atgggtgggg	ggcattccag	agcctctaag		1080
gtagccagtt	ctgttgccca	ttccccag	ctattaaacc	cttgatatgc	cccctaggcc		1140
tagtgggtgat	cccagtgctc	tactggggga	tgagagaaag	gcattttata	gcctgggcat		1200
aagtgaaatc	agcagagcct	ctgggtggat	gtgtagaagg	cacttcaaaa	tgcataaacc		1260
tgttacaatg	ttaaaaaaaa	aaaaaaaaaa					1289

<210> 112
 <211> 315
 <212> PRT
 <213> Homo sapien

<400> 112							
Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val Asn Lys Gln							
1 5 10 15							
Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys Asp Val Phe							
20 25 30							
Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr Gly Val Ala							
35 40 45							
Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro Ser Ile Leu							
50 55 60							
Arg Arg Val Phe Tyr Arg Pro Tyr Leu Gln Ile Phe Gly Gln Ile Pro							
65 70 75 80							
Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn Cys Ser Ser							
85 90 95							
Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala Gly Thr Cys							
100 105 110							
Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu Val Ile Phe							
115 120 125							
Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe							
130 135 140							

Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys
 145 150 155 160
 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu
 165 170 175
 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln
 180 185 190
 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu
 195 200 205
 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr
 210 215 220
 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp
 225 230 235 240
 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val
 245 250 255
 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg
 260 265 270
 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly
 275 280 285
 Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly
 290 295 300
 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp
 305 310 315

<210> 113

<211> 553

<212> PRT

<213> Homo sapien

<400> 113

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
 1 5 10 15
 Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu
 20 25 30
 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
 35 40 45
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly
 50 55 60
 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly
 65 70 75 80
 Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile
 85 90 95
 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu
 100 105 110
 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly
 115 120 125
 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu
 130 135 140
 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala
 145 150 155 160
 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr
 165 170 175
 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu
 180 185 190
 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu
 195 200 205
 Thr Cys Val Ala Ala Thr Leu Val Ala Glu Glu Ala Ala Leu Gly
 210 215 220
 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

[illegible]

```
<210> 114
<211> 241
<212> PRT
<213> Homo sapien
```

<400> 114															
Met	Gln	Cys	Phe	Ser	Phe	Ile	Lys	Thr	Met	Met	Ile	Leu	Phe	Asn	Leu
1				5					10					15	
Leu	Ile	Phe	Leu	Cys	Gly	Ala	Ala	Leu	Leu	Ala	Val	Gly	Ile	Trp	Val
			20					25					30		
Ser	Ile	Asp	Gly	Ala	Ser	Phe	Leu	Lys	Ile	Phe	Gly	Pro	Leu	Ser	Ser
		35					40					45			
Ser	Ala	Met	Gln	Phe	Val	Asn	Val	Gly	Tyr	Phe	Leu	Ile	Ala	Ala	Gly
	50					55					60				
Val	Val	Val	Phe	Ala	Leu	Gly	Phe	Leu	Gly	Cys	Tyr	Gly	Ala	Lys	Thr
65					70					75					80


```

Glu Ser Lys Cys Ala Leu Val Thr Ph Phe Phe Ile Leu Leu Leu Ile
      85                      90                      95
Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
      100                    105                    110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
      115                    120                    125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
      130                    135                    140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
      145                    150                    155                    160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
      165                    170                    175
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
      180                    185                    190
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
      195                    200                    205
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
      210                    215                    220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
      225                    230                    235                    240
Gln

```

```

<210> 115
<211> 366
<212> DNA
<213> Homo sapien

```

```

<400> 115
gctctttctc tccctcctc tgaatttaat tctttcaact tgcaatttgc aaggattaca      60
catttcactg tgaatgtatat tgtgttgcaa aaaaaaaaaa gtgtctttgt ttaaaattac      120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga      180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggaga attggatggg      240
tctcagaacc atttcaccca gacagcctgt ttctatcctg ttttaataaat tagtttgggt      300
tctctacatg cataacaaac cctgctccaa tctgtcacat aaaagtctgt gacttgaagt      360
ttagtc

```

```

<210> 116
<211> 282
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

```

```

<400> 116
acaaagatga accatttcct atattatagc aaaattaaaa tctaccogta ttctaattatt      60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa      120
agactttact attttcatat ttttaagacac atgattttat ctatttttagt aacctgggtc      180
atacggtaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt      240
tcaatctnga actatctana tcacagacat ttctatttcct tt

```

```

<210> 117
<211> 305
<212> DNA
<213> Homo sapien

```

<220>
 <221> misc_feature
 <222> (1)...(305)
 <223> n = A,T,C or G

<400> 117
 acacatgtcg cttcactgcc ttcttagatg cttctgggtca acatanagga acagggacca 60
 tattttatcct cctccttgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa 120
 aataaggcaa aatatatgaa acaacagggtc tcgagatatt ggaaatcagt caatgaagga 180
 tactgatccc tgatcactgt cctaattgcag gatgtgggaa acagatgagg tcacctctgt 240
 gactgccccca gottactgcc tgtagagagt ttctangctg cagttcagac agggagaaat 300
 tgggt 305

<210> 118
 <211> 71
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(71)
 <223> n = A,T,C or G

<400> 118
 accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa 60
 aantcctggt t 71

<210> 119
 <211> 212
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(212)
 <223> n = A,T,C or G

<400> 119
 actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca 60
 gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac 120
 agtaagctgg cccttctaataaaaagaaaat tgaaagggtt ctcactaanc ggaattaant 180
 aatggantca aganactccc aggcctcagc gt 212

<210> 120
 <211> 90
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(90)
 <223> n = A,T,C or G

<400> 120
 actcgttgca natcaggggc ccccagagt caccgttgca ggagtccttc tggctcttgcc 60
 ctccgccggc gcagaacatg ctgggggtgg 90

<210> 121
 <211> 218
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(218)
 <223> n = A,T,C or G

<400> 121
 tgtancgtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga 60
 gaataagatt tgctaaaaga ttgggggcta aaacatgggt attgggagac atttctgaag 120
 atatncangt aaattangga atgaattcat ggttcttttg ggaattcctt tacgatngcc 180
 agcatanact tcatgtgggg atancagcta cccttgta 218

<210> 122
 <211> 171
 <212> DNA
 <213> Homo sapien

<400> 122
 taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg 60
 catttgtag ctcatggaac aggaagtcgg atggtggggc atcttcagtg ctgcatgagt 120
 caccaccccg gcgggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t 171

<210> 123
 <211> 76
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(76)
 <223> n = A,T,C or G

<400> 123
 tgtagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca 60
 ttatcaanta ttgtgt 76

<210> 124
 <211> 131
 <212> DNA
 <213> Homo sapien

<400> 124
 acctttcccc aaggccaatg tctgtgtgta taactggccg gctgcaggac agctgcaatt 60
 caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120
 ttaagatttg t 131

<210> 125
 <211> 432
 <212> DNA
 <213> Homo sapien

<400> 125
 actttatcta ctggctatga aatagatggt ggaaaattgc gttaccaact ataccactgg 60
 cttgaaaaag aggtgatagc tcttcagagg acttgtgact ttgctcaga tgctgaagaa 120

```

ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat      180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg      240
ctcttgaagt atcagtcact tttagaatg tttcttagtt actgcatact tcatggatcc      300
catggtgggg gtcttgcacg tgtaagaatg gaattgattt tgcttttgca agaattctcag      360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaaccctc agtgcctctc      420
ctctttgctt gt                                     432

```

```

<210> 126
<211> 112
<212> DNA
<213> Homo sapien

```

```

<400> 126
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaaccat      60
agtaagaatg atatttcccc ccagggatca ccaaataatt ataaaaattt gt          112

```

```

<210> 127
<211> 54
<212> DNA
<213> Homo sapien

```

```

<400> 127
accacgaaac cacaacaag atggaagcat caatccactt gccaaagcaca gcag          54

```

```

<210> 128
<211> 323
<212> DNA
<213> Homo sapien

```

```

<400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctccctt ctaccagctc      60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca      120
ttctctctga agtctagggt acccattttg gggaccatt ataggcaata aacacagtgc      180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tottagcctt      240
ttctgcaaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct      300
aggctgcctt cttttccatg tcc                                     323

```

```

<210> 129
<211> 192
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(192)
<223> n = A,T,C or G

```

```

<400> 129
acatacatgt gtgtatattt ttaaataatca cttttgtatc actctgactt tttagcatat      60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc      120
tagcacattc atctgtgata naaagatagg tgagtttcat ttcttccacg ttggccaatg      180
gataaacaaa gt                                     192

```

```

<210> 130
<211> 362
<212> DNA
<213> Homo sapien

```

<220>
 <221> misc_feature
 <222> (1)...(362)
 <223> n = A,T,C or G

<400> 130
 ccctttttta tggaatgagt agactgtatg ttggaanatt tanccacaac ctcttttgaca 60
 tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa 120
 gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa 180
 ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata 240
 cttattttaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcaacttat 300
 tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatttta aaaagtaatg 360
 gg 362

<210> 131
 <211> 332
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(332)
 <223> n = A,T,C or G

<400> 131
 ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca 60
 gtangactgg tatgggttga gctgtccaga taaaaacatt tgaagagctc caaaatgaga 120
 gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc 180
 ttctgaacta gattaaggca gcttgtaa atctgatgtat ttggtttatt atccaactaa 240
 cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc 300
 atanaaggat tgggtgaagc tggcgttgtg gt 332

<210> 132
 <211> 322
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(322)
 <223> n = A,T,C or G

<400> 132
 actttttgcca ttttgtatat ataaacaatc ttgggacatt ctcctgaaaa ctaggtgtcc 60
 agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat 120
 ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggaccttg tatctcgggt 180
 tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg 240
 ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct aggggaagcct 300
 gtaacaatct acaattggtc ca 322

<210> 133
 <211> 278
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(278)

<223> n = A,T,C or G

<400> 133

acaagccttc	acaagtttaa	ctaaattggg	attaatcttt	ctgtanttat	ctgcataatt	60
cttggttttc	tttccatctg	gctcctgggt	tgacaatttg	tggaacaac	tctattgcta	120
ctatttaaaa	aaaatcacaa	atctttccct	ttaagctatg	ttnaattcaa	actattcctg	180
ctattcctgt	tttgtcaaag	aaattatatt	tttcaaaata	tgtntatttg	tttgatgggt	240
cccacgaac	actaataaaa	accacagaga	ccagcctg			278

<210> 134

<211> 121

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(121)

<223> n = A,T,C or G

<400> 134

gtttanaaaa	cttgtttagc	tccatagagg	aaagaatggt	aaactttgta	ttttaaaaca	60
tgattctctg	aggttaaact	tggttttcaa	atgttatatt	tacttgtatt	ttgcttttgg	120
t						121

<210> 135

<211> 350

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(350)

<223> n = A,T,C or G

<400> 135

acttanaacc	atgcctagca	catcagaatc	cctcaaagaa	catcagtata	atcctataacc	60
atancaagtg	gtgactgggt	aagcgtgcga	caaagggtcag	ctggcacatt	acttgtgtgc	120
aaacttgata	cttttgttct	aagtaggaac	tagtatacag	tnccctaggan	tggtactcca	180
gggtgcccc	caactcctgc	agccgctcct	ctgtgccagn	ccctgnaagg	aactttcgct	240
ccacctcaat	caagccctgg	gccatgctac	ctgcaattgg	ctgaacaaac	gtttgctgag	300
ttccaagga	tgcaaagcct	gggtgctcaac	tcctggggcg	tcaactcagt		350

<210> 136

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(399)

<223> n = A,T,C or G

<400> 136

tgtaccgtga	agacgacaga	agttgcatgg	cagggacagg	gcagggccga	ggccagggtt	60
gctgtgattg	tatccgaata	ntcctcgtga	gaaaagataa	tgagatgacg	tgagcagcct	120
gcagacttgt	gtctgccttc	aanaagccag	acaggaaggc	cctgcctgcc	ttggctctga	180
cctggcggcc	agccagccag	ccacaggtgg	gcttcttctt	tttgtggtga	caacnccaag	240
aaaactgcag	aggcccaggg	tcaggtgtna	gtgggtangt	gaccataaaa	caccaggtgc	300

tcccaggaac cccgggcaaag gccatcccca cctacagcca gcatgcccac tggcgtgatg	360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt	399

<210> 137
 <211> 165
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(165)
 <223> n = A,T,C or G

<400> 137	
actggtgtgg tnggggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt	60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga	120
ttggtgtgtc ccaactggtg tcactgtcat tgggtggggt cctgt	165

<210> 138
 <211> 338
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(338)
 <223> n = A,T,C or G

<400> 138	
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc	60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgoccaa	120
tgctgggcag tctcccatgc cttccacagt gaaagggtt gagaaaaatc acatccaatg	180
tcatgtgttt ccagccacac caaaagggtc ttgggggtgga gggctggggg catananggt	240
cangcctcag gaagcctcaa gttccattca gctttgccac tgtacattcc ccatntttaa	300
aaaaactgat gccttttttt tttttttttg taaaattc	338

<210> 139
 <211> 382
 <212> DNA
 <213> Homo sapien

<400> 139	
gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa	60
gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccga gtgaaggaga	120
attcaaacag acctcgtcat tcttggtgtg agcctggtcg gctcaccgcc tatcatctgc	180
atttgctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg	240
ccttatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat	300
gtcagctatg tgccccatcc tccttcacgc cctccctccc tttcctacca ctgctgagt	360
gcctggaact tgtttaaagt gt	382

<210> 140
 <211> 200
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(200)

<223> n = A,T,C or G

<400> 140

acccaaancctt	ctttctgttg	tggtngattt	tactataggg	gtttngcttn	ttctaaanat	60
acttttcatt	taacancctt	tgtaagtgt	caggctgcac	tttgcctcat	anaattattg	120
ttttcacatt	tcaacttgta	tggtgttgct	tcttanagca	ttggtgaaat	cacatatttt	180
atattcagca	taaaggagaa					200

<210> 141

<211> 335

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(335)

<223> n = A,T,C or G

<400> 141

actttatttt	caaaacactc	atatgttgca	aaaaacacat	agaaaaataa	agtttggtgg	60
gggtgctgac	taaacttcaa	gtcacagact	tttatgtgac	agattggagc	agggtttggt	120
atgcatgtag	agaaccctaaa	ctaattttatt	aaacaggata	gaaacaggct	gtctgggtga	180
aatgggtctg	agaaccatcc	aattcacctg	tcagatgctg	atanactagc	tcttcagatg	240
tttttctacc	agttcagaga	tnggttaatg	actanttcca	atggggaaaa	agcaagatgg	300
attcacaac	caagtaattt	taaacaaaga	cactt			335

<210> 142

<211> 459

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(459)

<223> n = A,T,C or G

<400> 142

accagggttaa	tattgccaca	tatatccttt	ccaattgcgg	gctaaacaga	cgtgtattta	60
gggttggtta	aagacaaccc	agcttaatat	caagagaaat	tgtgaccttt	catggagtat	120
ctgatggaga	aaacactgag	ttttgacaaa	tcttatttta	ttcagatagc	agtctgatca	180
cacatggtcc	aacaacactc	aaataataaa	tcaaataatna	tcagatgtta	aagattggtc	240
ttcaaacatc	atagccaatg	atgcccgcgt	tgctataat	ctctccgaca	taaaaccaca	300
tcaacacctc	agtggccacc	aaaccattca	gcacagcttc	cttaactgtg	agctgtttga	360
agctaccagt	ctgagcacta	ttgactatnt	ttttcangct	ctgaatagct	ctagggatct	420
cagcangggg	gggaggaacc	agctcaacct	tggcgtant			459

<210> 143

<211> 140

<212> DNA

<213> Homo sapien

<400> 143

acatttcctt	ccaccaagtc	aggactcctg	gcttctgtgg	gagttcttat	cacctgaggg	60
aatccaaac	agtctctcct	agaaaggaat	agtgtcacca	acccacacca	tctccctgag	120
accatccgac	ttccctgtgt					140

<210> 144

<211> 164

<212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(164)
 <223> n = A,T,C or G

<400> 144
 acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct 60
 atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaaattg 120
 aggcaattaa tccatatttg ttttcaataa ggaaaaaaag atgt 164

<210> 145
 <211> 303
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(303)
 <223> n = A,T,C or G

<400> 145
 acgtagacca tccaactttg tatttghtaat ggcaaacatc cagnagcaat tcctaaacaa 60
 actggagggt atttataccc aattatccca ttcattaaca tgccctcttc ctccaggctat 120
 gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca 180
 gtaggggagt ccatccaagt gacagggtcta atcaaaggag gaaatggaac ataagcccag 240
 tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat 300
 caa 303

<210> 146
 <211> 327
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(327)
 <223> n = A,T,C or G

<400> 146
 actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac 60
 actggcctgg agtgactcat tgctctggtt ggttgagaga gtccttttgc caacaggcct 120
 ccaagtcagg gctgggattt gtttccttcc cacattctag caacaatatg ctggccactt 180
 cctgaacagg gaggggtgga ggagccagca tggaacaagc tgccacttcc taaagtagcc 240
 agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg 300
 taggggtgag ctgtgtgact ctatggt 327

<210> 147
 <211> 173
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(173)
 <223> n = A,T,C or G

<400> 147
 acattgtttt tttagataa agcattgana gagctctcct taaogtgaca caatggaagg 60
 actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120
 atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt 173

<210> 148
 <211> 477
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(477)
 <223> n = A,T,C or G

<400> 148
 acaaccactt tatctcatcg aattttttaac ccaaactcac tcactgtgcc tttctatcct 60
 atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcactact 120
 gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg 180
 gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac 240
 nccanccac ctccaccgacc ccatcctctt acacagctac ctccctgtct tctaacccca 300
 tagattatnt ccaaattcag tcaattaagt tactattaac actctaccgg acatgtccag 360
 caccactggt aagccttctc cagccaacac acacacacac acacncacac acacacatat 420
 ccaggcacag gctacctcat cttcacatc acccctttaa ttaccatgct atggtgg 477

<210> 149
 <211> 207
 <212> DNA
 <213> Homo sapien

<400> 149
 acagttgtat tataatatca agaaataaac ttgcaatgag agcattttaag agggaagaac 60
 taacgtatatt tagagagcca aggaagggtt ctgtgggggag tgggatgtaa ggtggggcct 120
 gatgataaat aagagtcagc caggttaagt ggtggtgtgg tatgggcaca gtgaagaaca 180
 tttcaggcag agggaacagc agtgaaa 207

<210> 150
 <211> 111
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(111)
 <223> n = A,T,C or G

<400> 150
 acottgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg 60
 cacttaaagt tggtcagtgt ttggacttgt taactantgg catctttggg t 111

<210> 151
 <211> 196
 <212> DNA
 <213> Homo sapien

<400> 151
 agcgcggcag gtcattatga acattccaga tacctatcat tactcgatgc tgttgataac 60

agcaagatgg	ctttgaactc	agggtcacca	ccagctattg	gaccttacta	tgaaaacccat	120
ggataccaac	cggaaaaccc	ctatcccgca	cagcccactg	tggtccccac	tgtctacgag	180
gtgcatccgg	ctcagt					196

<210> 152
 <211> 132
 <212> DNA
 <213> Homo sapien

<400> 152						
acagcacttt	cacatgtaag	aagggagaaa	ttcctaaatg	taggagaaag	ataacagAAC	60
cttccccttt	tcatctagt	gtggaaacct	gatgctttat	gttgacagga	atagaaccag	120
gagggagttt	gt					132

<210> 153
 <211> 285
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(285)
 <223> n = A,T,C or G

<400> 153						
acaanaccCa	nganaggcca	ctggccgtgg	tgtcatggcc	tccaaacatg	aaagtgtcag	60
cttctgtctt	tatgtcctca	tctgacaact	ctttaccatt	tttatcctcg	ctcagcagga	120
gcacatcaat	aaagtccaaa	gtcttggaact	tggccttggc	ttggaggaag	tcatcaaac	180
cctggctagt	gaggggtgcg	cgccgctcct	ggatgacggc	atctgtgaag	tcgtgcacca	240
gtctgcaggc	cctgtggaag	cgccgtccac	acggagtnag	gaatt		285

<210> 154
 <211> 333
 <212> DNA
 <213> Homo sapien

<400> 154						
accacagtcc	tggtgggcca	gggcttcatt	accctttctg	tgaaaagcca	tattatcacc	60
accccaaatt	tttctttaa	tatctttaac	tgaaggggtc	agcctcttga	ctgcaaagac	120
cctaagccgg	ttacacagct	aactcccact	ggccctgatt	tgtgaaattg	ctgctgcctg	180
attggcacag	gagtcgaagg	tggtcagctc	ccctcctccg	tggaacgaga	ctctgatttg	240
agtttcacaa	attctcgggc	cacctcgtca	ttgctcctct	gaaataaaat	ccggagaatg	300
gtcaggcctg	tctcatccat	atggatcttc	cgg			333

<210> 155
 <211> 308
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(308)
 <223> n = A,T,C or G

<400> 155						
actggaaata	ataaaaacca	catcacagt	ttgtgtcaaa	gatcatcagg	gcatggatgg	60
gaaagtgtt	tgggaactgt	aaagtgccta	acacatgatc	gatgattttt	gttataatat	120
ttgaatcacg	gtgcatataa	actctcctgc	ctgctcctcc	tgggccccag	ccccagcccc	180

atcacagctc actgctctgt tcatccaggc ccagcatgta gtggctgatt cttcttggt 240
 gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcattgctg 300
 gccctggt 308

<210> 156
 <211> 295
 <212> DNA
 <213> Homo sapien

<400> 156
 accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta 60
 ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga 120
 gaataggaga ttatgtttgg cctcatatt ctctcctatc ctcttgctt cattctatgt 180
 ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat 240
 aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat 295

<210> 157
 <211> 126
 <212> DNA
 <213> Homo sapien

<400> 157
 acaagtttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct 60
 gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc 120
 cttagt 126

<210> 158
 <211> 442
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(442)
 <223> n = A,T,C or G

<400> 158
 acccaactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg 60
 aancagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt 120
 gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatat 180
 ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta 240
 natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtgtg 300
 ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga 360
 nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg 420
 tgttcattct ctgatgtcct gt 442

<210> 159
 <211> 498
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(498)
 <223> n = A,T,C or G

<400> 159
 acttcagggt aacgttggtt tttccgttga gcctgaactg atgggtgacg ttgtagggtc 60

tccaacaaga	actgaggttg	cagagcgggt	agggagaggt	gctgttccag	ttgcacctgg	120
gctgctgtgg	actgttggtg	attcctcaact	acggcccaag	gttggtgaac	tgccanaaag	180
gtgtgtgtgt	gganttgagc	tcgggcgggt	gtggtaggtt	gtgggctctt	caacaggggc	240
tgctgtggtg	ccgggangtg	aangtggttg	gtcacttgag	cttggccagc	tctggaaagt	300
antanattct	tcctgaaggc	cagcgcttgt	ggagctggca	ngggtcantg	ttgtgtgtaa	360
cgaaccagtg	ctgctgtggg	tgggtgtana	tcctccacaa	agcctgaagt	tatggtgtcn	420
tcaggtaana	atgtggtttc	agtgtccctg	ggcngctgtg	gaagggttga	nattgtcacc	480
aagggaataa	gctgtggt					498

<210> 160

<211> 380

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(380)

<223> n = A,T,C or G

<400> 160

acctgcatcc	agcttccctg	ccaaactcac	aaggagacat	caacctctag	acagggaaac	60
agcttcagga	tacttccagg	agacagagcc	accagcagca	aaacaaatat	tcccatgcct	120
ggagcatggc	atagaggaag	ctganaaatg	tggggtctga	ggaagccatt	tgagtctggc	180
cactagacat	ctcatcagcc	acttgtgtga	agagatgccc	catgacccca	gatgcctctc	240
ccacccttac	ctccatctca	cacacttgag	ctttccactc	tgtataattc	taacatcctg	300
gagaaaaatg	gcagtttgac	cgaacctgtt	cacaacggtg	gaggctgatt	tctaacgaaa	360
cttgtagaat	gaagcctgga					380

<210> 161

<211> 114

<212> DNA

<213> Homo sapien

<400> 161

actccacatc	ccctctgagc	aggcgggttg	cgttcaaggt	gtatttggcc	ttgcctgtca	60
cactgtccac	tggcccctta	tccacttggt	gcttaatccc	tcgaaagagc	atgt	114

<210> 162

<211> 177

<212> DNA

<213> Homo sapien

<400> 162

actttctgaa	tcgaatcaaa	tgatacttag	tgtagtttta	atatcctcat	atatatcaaa	60
gttttactac	tctgataatt	ttgtaaacca	ggttaaccaga	acatccagtc	atacagcttt	120
tggtgatata	taacttggca	ataacccagt	ctggtgatac	ataaaactac	tcactgt	177

<210> 163

<211> 137

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(137)

<223> n = A,T,C or G

<400> 163

catttatata gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac 60
 canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt 120
 catcagcggc atgatgt 137

<210> 164
 <211> 469
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(469)
 <223> n = A,T,C or G

<400> 164
 cttatcacia tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta 60
 tgcaatgcat catgctatct catacctaata gagggagttc caggagattc aaccaggaaa 120
 tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt 180
 gagacatgca cttgctacga aacagaaatt tcatgttgca cccttggttc tacacctgtg 240
 ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg 300
 gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct 360
 tctagtaggc acagggtcc caggccaggc ctcattctcc tctggcctct aatagtcaat 420
 gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt 469

<210> 165
 <211> 195
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(195)
 <223> n = A,T,C or G

<400> 165
 acagtttttt atatatatcg acattgcggc caatttgtgt cagtttcata aagctgggtgg 60
 atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc 120
 tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact 180
 tcctctgaga tgagt 195

<210> 166
 <211> 383
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(383)
 <223> n = A,T,C or G

<400> 166
 acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc 60
 cgaggtcgga gtccacacca ccggtgtagg tgtgtctcaat cttgggcttg gcgcccacct 120
 ttggagaagg gatattgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt 180
 tttgcagacc agcctgagca aggggcggat gttcagcttc agtcctcct tcgtcagggtg 240
 gatgccaacc tcgtctangg tccgtgggaa gctgggtgtcc acntcaccta caacctgggc 300
 gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt 360
 nggggccttt ttggtgaact ttc 383

<210> 167
 <211> 247
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(247)
 <223> n = A,T,C or G

<400> 167
 acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat 60
 tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc 120
 tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac 180
 tcaatctgan tccaaagtgg tggttggaac actggtcatg acanaggcag tgactctgac 240
 tgangtc 247

<210> 168
 <211> 273
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(273)
 <223> n = A,T,C or G

<400> 168
 acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg ttacttcaa 60
 aatccctcan ccttggtctt cactactgtc tatactgana gtgtcatgtt tccacaaagg 120
 gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag taggggtgggc 180
 aattcccaac ttccttgcca caagcttccc aggccttctc ccctggaaaa ctccagcttg 240
 agtcccagat acactcatgg gctgccttgg gca 273

<210> 169
 <211> 431
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(431)
 <223> n = A,T,C or G

<400> 169
 acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60
 agctcagacc aggggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120
 ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagtttg cacaggtgag 180
 ggcagcagaa aggggggtant tactgatgga caccatcttc tctgtatact ccacactgac 240
 cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcaactgctgg gcaccagctc 300
 acgcacatca ctgacaaccg ggatggaaaa agaantgcc aactttcatac atccaactgg 360
 aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420
 tcgaacactg a 431

<210> 170
 <211> 266
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(266)

<223> n = A,T,C or G

<400> 170

acctgtgggc	tggtgtgta	tgctgtgcc	ggctgtgaa	agggagttca	gaggtggagc	60
tcaaggagct	ctgcaggcat	tttgccaanc	ctctccanag	canagggagc	aacctacact	120
ccccgctaga	aagacaccag	attggagtcc	tgggaggggg	agttgggggtg	ggcatttgat	180
gtatacttgt	cacctgaatg	aangagccag	agaggaanga	gacgaanatg	anattggcct	240
tcaaagctag	gggtctggca	ggtgga				266

<210> 171

<211> 1248

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1248)

<223> n = A,T,C or G

<400> 171

ggcagccaaa	tcataaacgg	cgaggactgc	agcccgcact	cgcagccctg	gcaggcggca	60
ctggatcatg	aaaacgaatt	gttctgctcg	ggcgctctgg	tgcatccgca	gtgggtgctg	120
tcagccgcac	actgtttcca	gaagtgagtg	cagagctcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccaggg	agccagatgg	tggaggccag	cctctccgta	240
cggcaccag	agtacaacag	acccttgctc	gctaacgacc	tcagtctcat	caagttggac	300
gaatccgtgt	ccgagtctga	caccatccgg	agcatcagca	ttgtttcgca	gtgccctacc	360
gcggggaaact	cttgctctgt	ttctggctgg	ggtctgctgg	cgaacggcag	aatgcctacc	420
gtgctgcagt	gcgtgaacgt	gtcgggtggtg	tctgaggagg	tctgcagtaa	gctctatgac	480
ccgctgtacc	accccagcat	gttctgcgcc	ggcgaggagg	aagaccagaa	ggactcctgc	540
aacggtgact	ctggggggcc	cctgatctgc	aacgggtact	tgacgggcct	tgtgtctttc	600
ggaaaagccc	cgtgtggcca	agttggcgtg	ccagggtgtct	acaccaacct	ctgcaaattc	660
actgagtggg	tagagaaaac	cgtccaggcc	agtttaactct	ggggactggg	aacccatgaa	720
attgaccccc	aaatacatcc	tgcggaagga	attcaggaat	atctgttccc	agccccctct	780
ccctcaggcc	caggagtcca	ggccccagc	ccctcctccc	tcaaaccaag	ggtacagatc	840
cccagcccc	cctccctcag	acccaggagt	ccagaccccc	cagccccctc	tccctcagac	900
ccaggagtcc	agccccctct	ccctcagacc	caggagtcca	gacccccag	cccctcctcc	960
ctcagaccca	ggggtccagg	cccccaaccc	ctcctccctc	agactcagag	gtccaagccc	1020
ccaaccntc	attccccaga	cccagaggtc	cagggtcccag	cccctcntcc	ctcagaccca	1080
gcggtccaat	gccacctaga	ctntccctgt	acacagtgcc	cccttggtgg	acgttgaccc	1140
aaccttacca	gttggttttt	catttttngt	ccctttcccc	tagatccaga	aataaagttt	1200
aagagaagng	caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaa		1248

<210> 172

<211> 159

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(159)

<223> Xaa = Any Amino Acid

<400> 172

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
 1 5 10 15
 Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
 20 25 30
 Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
 35 40 45
 Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
 50 55 60
 Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
 65 70 75 80
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
 85 90 95
 Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
 100 105 110
 Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
 115 120 125
 Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
 130 135 140
 Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 145 150 155

<210> 173
 <211> 1265
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(1265)
 <223> n = A,T,C or G

<400> 173
 ggcagcccgc actcgagccc ctggcaggcg geactgggtca tggaaaacga attgttctgc 60
 tcgggcgctcc tgggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc 120
 tacaccatcg ggctgggccc gcacagtctt gaggccgacc aagagccagg gagccagatg 180
 gtggaggcca gcctctccgt acggcaccca gactacaaca gaccttgct cgctaacgac 240
 ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc 300
 attgcttcgc agtgccctac cgcggggaac tcttgctctg tttctggctg ggggtctgctg 360
 gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtctc tgcccagtcg 420
 cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga 480
 acgtgtcggg ggtgtctgag gaggtctgca gtaagctcta tgaccgctg taccacccca 540
 gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg 600
 ggcccctgat ctgcaacggg tacttgacgg gccttggtgc tttcggaaaa gccccgtgtg 660
 gccaaagtgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga 720
 aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac 780
 atcctgcgga aggaattcag gaatatctgt tcccagcccc tctcctcaga ggcccaggag 840
 tccaggcccc cagccccctc tccctcaaac caagggtaca gatccccagc cctcctctcc 900
 tcagaccag gagtccagac cccccagccc ctctcctc agaccagga gtccagcccc 960
 tctcctntca gaccagggag tccagacccc ccagcccctc ctccctcaga cccaggggtt 1020
 gagggcccca acccctcctc cttcagagtc agagggtcaa gcccacaacc cctcgttccc 1080
 cagaccaga ggtnnaggtc ccagcccctc ttcctcaga cccagnggtc caatgccacc 1140
 tagattttcc ctgnacacag tgcccccttg tggngangttg acccaacctt accagttggt 1200
 ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa 1260
 aaaaa 1265

<210> 174
 <211> 1459
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1459)

<223> n = A,T,C or G

<400> 174

ggtcagccgc	acactgtttc	cagaagtgcg	tgcagagctc	ctacaccatc	gggctgggccc	60
tgcacagtct	tgaggccgac	caagagccag	ggagccagat	ggtggaggcc	agcctctccg	120
tacggcacc	agagtacaac	agacccttgc	tcgctaacga	cctcatgctc	atcaagttgg	180
acgaatccgt	gtccgagttc	gacaccatcc	ggagcatcag	cattgcttcg	cagtgcctta	240
ccgcggggaa	ctcttgccctc	gtttctggct	ggggtctgct	ggcgaacggg	gagctcacgg	300
gtgtgtgtct	gccctcttca	aggaggtcct	ctgcccagtc	gcgggggctg	acccagagct	360
ctgcgtccca	ggcagaatgc	ctaccgtgct	gcagtgcgtg	aacgtgtcgg	tggtgtctga	420
ngaggtctgc	antaagctct	atgaccgcgt	gtaccacccc	ancatgttct	gcgcccggcg	480
agggcaagac	cagaaggact	cctgcaacgt	gagagagggg	aaaggggagg	gcaggcgact	540
caggggaagg	tggagaagg	ggagacagag	acacacaggg	ccgcatggcg	agatgcagag	600
atggagagac	acacagggag	acagtgacaa	ctagagagag	aaactgagag	aaacagagaa	660
ataaacacag	gaataaagag	aagcaaagga	agagagaaac	agaaacagac	atggggaggc	720
agaaacacac	acacatagaa	atgcagttga	ccttccaaca	gcatggggcc	tgagggcggg	780
gacctccacc	caatagaaaa	tcctcttata	acttttgact	ccccaaaaac	ctgactagaa	840
atagcctact	gttgacgggg	agccttacca	ataacataaa	tagtcgattt	atgcatacgt	900
tttatgcatt	catgatatac	ctttgttgga	attttttgat	atttctaagc	tacacagttc	960
gtctgtgaat	tttttttaaat	tgttgcaact	ctcctaaaat	ttttctgatg	tgtttattga	1020
aaaaatccaa	gtataagtgg	acttgtgcat	tcaaaccagg	gttggtcaag	ggtcaactgt	1080
gtacccagag	ggaaacagtg	acacagattc	atagaggtga	aacacgaaga	gaaacaggaa	1140
aatcaagac	tctacaaaga	ggctgggcag	ggtggctcat	gcctgtaate	ccagcacttt	1200
gggaggcgag	gcaggcagat	cacttgagg	aaggagttca	agaccagcct	ggccaaaatg	1260
gtgaaatcct	gtctgtacta	aaaatacaaa	agtaagtctg	atatggtggc	aggcgctgt	1320
aatcccagct	acttgggagg	ctgaggcagg	agaattgctt	gaatatggga	ggcagaggtt	1380
gaagtgaagt	gagatcacac	cactatactc	cagctggggc	aacagagtaa	gactctgtct	1440
caaaaaaaaa	aaaaaaaaa					1459

<210> 175

<211> 1167

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1167)

<223> n = A,T,C or G

<400> 175

gcgcagccct	ggcaggcggc	actggtcatg	gaaaacgaat	tgttctgctc	gggcgtcctg	60
gtgcatccgc	agtgggtgct	gtcagccgca	cactgtttcc	agaactccta	caccatcggg	120
ctgggcctgc	acagctctga	ggccgaccaa	gagccaggga	gccagatggg	ggaggccagc	180
ctctccgtac	ggcaccaga	gtacaacaga	ctcttgctcg	ctaaccgact	catgctcatc	240
aagttggacg	aatccgtgtc	cgagtctgac	accatccgga	gcatcagcat	tgcttcgcag	300
tgccctaccg	cggggaactc	ttgcctcgtn	tctggctggg	gtctgctggc	gaacggcaga	360
atgcctaccg	tgctgcactg	cgtgaacgtg	tcggtgggtg	ctgaggangt	ctgcagtaag	420
ctctatgacc	cgctgtacca	ccccagcatg	ttctgcgccg	gcggagggca	agaccagaag	480
gactcctgca	acggtgactc	tggggggccc	ctgatctgca	acgggtactt	gcagggcctt	540
gtgtctttcg	gaaaagcccc	gtgtggccaa	cttggcgtgc	caggtgtcta	caccaacctc	600
tgcaaattca	ctgagtggat	agagaaaacc	gtccagncca	gttaactctg	gggactggga	660
acccatgaaa	ttgaccccca	aatacatcct	gcggaangaa	ttcaggaata	totgttccca	720
gcccctcctc	cctcaggccc	aggagtccag	gccccagccc	cctcctccct	caaaccaagg	780

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gtacagatcc ccagcccctc ctccctcaga cccaggagtc cagaccccc agccccctcnt 840
ccntcagacc caggagtcca gccctcctc cntcagacgc aggagtccag accccccagc 900
ccntcntccg tcagaccagc ggggtgcaggc ccccaacccc tcntccntca gagtccagagg 960
tccaagcccc caacccctcg ttccccagac ccagagggtnc aggtcccagc ccctcctccc 1020
tcagaccagc cgggtccaatg ccacctagan tntccctgta cacagtgcc ccttggtggca 1080
ngttgaccca accttaccag ttgggttttc attttttgtc cctttcccct agatccagaa 1140
ataaagtnta agagaagcgc aaaaaaa 1167

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<210> 176
 <211> 205
 <212> PRT
 <213> Homo sapien

<220>
 <221> VARIANT
 <222> (1)...(205)
 <223> Xaa = Any Amino Acid

<400> 176

Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp
1				5					10					15	
Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
			20					25					30		
Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val
		35					40					45			
Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Leu	Leu	Leu
	50					55					60				
Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu	Ser
65					70				75					80	
Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala	Gly
			85					90						95	
Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg	Met
			100					105					110		
Pro	Thr	Val	Leu	His	Cys	Val	Asn	Val	Ser	Val	Val	Ser	Glu	Xaa	Val
		115					120					125			
Cys	Ser	Lys	Leu	Tyr	Asp	Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys	Ala
		130				135					140				
Gly	Gly	Gly	Gln	Asp	Gln	Lys	Asp	Ser	Cys	Asn	Gly	Asp	Ser	Gly	Gly
145					150					155				160	
Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu	Val	Ser	Phe	Gly	Lys
			165					170						175	
Ala	Pro	Cys	Gly	Gln	Leu	Gly	Val	Pro	Gly	Val	Tyr	Thr	Asn	Leu	Cys
			180					185					190		
Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Xaa	Ser			
		195					200					205			

<210> 177
 <211> 1119
 <212> DNA
 <213> Homo sapien

<400> 177

gcgcactcgc	agccctggca	ggcggcactg	gtcatggaaa	acgaattgtt	ctgctcgggc	60
gtcctgggtgc	atccgcagtg	ggtgctgtca	gccgcacact	gtttccagaa	ctcctacacc	120
atcgggctgg	gcctgcacag	tcttgaggcc	gaccaagagc	cagggagcca	gatggtggag	180
gccagcctct	ccgtacggca	cccagagtac	aacagaccct	tgctcgctaa	cgacctcatg	240
ctcatcaagt	tggacgaatc	cgtgtccgag	tctgacacca	tccggagcat	cagcattgct	300
tgcagtgcc	ctaccgcggg	gaactcttgc	ctcgtttctg	gctggggtct	gctggcgaac	360

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gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc 420
caaccctggc agggttgtac catttcggca acttccagtg caaggacgtc ctgctgcatc 480
ctcactgggt gtcactact gtcactgca tcacccggaa cactgtgatc aactagccag 540
caccatagtt tcccgaaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600
actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc 660
cagttatcct cactgaattg agatttcctg cttcagtgtc agccattccc acataatttc 720
tgacctacag aggtgaggga tcatatagct cttcaaggat gctgggtactc ccctcacaaa 780
ttcatttctc ctgttgtagt gaaagggtgcg ccctctggag cctcccaggg tgggtgtgca 840
ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900
ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960
accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg 1020
gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc 1080
ttaataaaca gaagctgtga tgtaaaaaa aaaaaaaa 1119

```

<210> 178
 <211> 164
 <212> PRT
 <213> Homo sapien

<220>
 <221> VARIANT
 <222> (1)...(164)
 <223> Xaa = Any Amino Acid

```

<400> 178
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1          5          10          15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
          20          25          30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
          35          40          45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
          50          55          60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
          65          70          75          80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
          85          90          95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
          100          105          110
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
          115          120          125
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
          130          135          140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Thr Ala Ser
          145          150          155          160
Pro Gly Thr Leu

```

<210> 179
 <211> 250
 <212> DNA
 <213> Homo sapien

```

<400> 179
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct 120
gccaggcact gttcatctca gcttttctgt ccctttgtct ccggcaagcg cttctgtctga 180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa 240

```

aaaaaaaaaa

250

<210> 180
 <211> 202
 <212> DNA
 <213> Homo sapien

<400> 180

actagtcacag	tgtggtggaa	ttccattgtg	ttgggcccaa	cacaatggct	acctttaaca	60
tcacccagac	cccgcccctg	cccgcgcccc	acgctgctgc	taacgacagt	atgatgctta	120
ctctgctact	cggaactat	ttttatgtaa	ttaatgtatg	ctttcttggt	tataaatgcc	180
tgatttaaaa	aaaaaaaaaa	aa				202

<210> 181
 <211> 558
 <212> DNA
 <213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(558)

<223> n = A,T,C or G

<400> 181

tccytttgkt	naggtttkkg	agacamccck	agacctwaan	ctgtgtcaca	gacttcyngg	60
aatgttttagg	cagtgcctagt	aatttcytcg	taatgattct	gttattactt	tcctnattct	120
ttattcctct	ttcttctgaa	gattaatgaa	gttgaaaatt	gaggtggata	aatacaaaaa	180
ggtagtgtga	tagtataagt	atctaagtcg	agatgaaagt	gtgttatata	tatccattca	240
aaattatgca	agttagtaat	tactcagggt	taactaaatt	actttaatat	gctgttgaac	300
ctactctgtt	ccttggtctag	aaaaaattat	aaacaggact	ttgttagttt	gggaagccaa	360
attgataata	ttctatgttc	taaaagttgg	gctatacata	aattattaag	aaatatggaw	420
ttttattccc	aggaatatgg	kgttcatttt	atgaatatta	cscrggatag	awgtwtgagt	480
aaaaycagtt	ttggtwaata	ygtwaatatg	tcmtaataaa	acaakgcttt	gactttattc	540
caaaaaaaaa	aaaaaaaa					558

<210> 182
 <211> 479
 <212> DNA
 <213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(479)

<223> n = A,T,C or G

<400> 182

acagggwttk	grggatgcta	agsccccrga	rwtygtttga	tccaaccctg	gcttwttttc	60
agaggggaaa	atggggccta	gaagttacag	mecatytagy	tggtgcgmg	gcacccctgg	120
cstcacacag	astcccagag	agctgggact	acaggcacac	agtcactgaa	gcaggccctg	180
ttwgcaattc	acgttgccac	ctccaactta	aacattcttc	atatgtgatg	tccttagtca	240
ctaaggttaa	actttccac	ccagaaaagg	caacttagat	aaaatcttag	agtactttca	300
tactmttcta	agtcctcttc	cagcctcact	kkgagtcctm	cytggggggt	gataggaant	360
ntctcttggc	tttctcaata	aartctctat	ycatctcatg	tttaatttgg	tacgcataara	420
awtgstgara	aaattaaaat	gttctgggtty	mactttaaaa	aaaaaaaaaa	aaaaaaaaaa	479

<210> 183
 <211> 384
 <212> DNA

<213> Homo sapien

<400> 183

aggcgggagc	agaagctaaa	gccaaagccc	aagaagagt	gcagtgccag	cactgggtgcc	60
agtaccagta	ccaataacag	tgccagtgcc	agtgccagca	ccagtgggtg	cttcagtgtc	120
ggtgccagcc	tgaccgccac	tctcacattt	gggtctctcg	ctggccttgg	tggagctggg	180
gccagcacca	gtggcagctc	tgggtgcctgt	ggtttctcct	acaagtgaga	ttttagatat	240
tgtaaatcct	gccagtcttt	ctcttcaagc	caggggtgcat	cctcagaaac	ctactcaaca	300
cagcactcta	ggcagccact	atcaatcaat	tgaagttgac	actctgcatt	aratctattt	360
gccatttcaa	aaaaaaaaaa	aaaa				384

<210> 184

<211> 496

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(496)

<223> n = A,T,C or G

<400> 184

accgaattgg	gaccgctggc	ttataagcga	tcattgtynt	ccrgtatcac	ctcaacgagc	60
aggagatc	agtctatacg	ctgaagaaat	ttgaccgat	gggacaacag	acctgctcag	120
cccctctgc	tcggttctcc	ccagatgaca	aatactctsg	acaccgaatc	accatcaaga	180
aacgcttcaa	ggtgctcatg	accagcaac	cgcgcctgt	cctctgaggg	tcccttaaac	240
tgatgtcttt	tctgccacct	gttaccctc	ggagactccg	taaccaaact	cttcggactg	300
tgagccctga	tgcctttttg	ccagccatac	tctttggcat	ccagtctctc	gtggcgattg	360
attatgcttg	tgtgaggcaa	tcattggtgg	atcacccata	aagggaacac	atttgacttt	420
ttttctcat	attttaaatt	actacmagaw	tattwmagaw	waaatgawtt	gaaaaactst	480
taaaaaaaaa	aaaaaa					496

<210> 185

<211> 384

<212> DNA

<213> Homo sapien

<400> 185

gctggtagcc	tatggcgkgg	cccacggagg	ggctcctgag	gccacggrac	agtgacttcc	60
caagtatcyt	gcgcsgcgtc	ttctaccgtc	cctacctgca	gatcttcggg	cagattcccc	120
aggaggacat	ggacgtggcc	ctcatggagc	acagcaactg	ytogtcggag	cccggcttct	180
gggcacaccc	tcctggggcc	caggcgggca	cctgcgtctc	ccagtatgcc	aactggctgg	240
tgggtgctgt	cctcgtcatc	ttcctgctcg	tggccaacat	cctgctgggtc	aacttgctca	300
ttgccatgtt	cagttacaca	ttcggcaaag	tacagggcaa	cagcgatctc	tactgggaag	360
gcgcagcgtt	accgcctcat	ccgg				384

<210> 186

<211> 577

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(577)

<223> n = A,T,C or G

<400> 186

gagttagctc	ctccacaacc	ttgatgaggt	cgtctgcagt	ggcctctcgc	ttcataccgc	60
------------	------------	------------	------------	------------	------------	----

tnccatcgtc	atactgtagg	tttgccacca	cytcctggca	tcttggggcg	gcntaatatt	120
ccaggaaact	ctcaatcaag	tcaccgtcga	tgaaacctgt	gggctgggtc	tgtcttccgc	180
tcggtgtgaa	aggatctccc	agaaggagt	ctcgatcttc	cccacacttt	tgatgacttt	240
attgagtcga	ttctgcatgt	ccagcaggag	gttgtaggag	ctctctgaca	gtgagggtcac	300
cagccctatc	atgccgttga	mcgtgccgaa	garcaccgag	ccttgtgtgg	gggkkgaa	360
ctcaccaga	ttctgcatta	ccagagagcc	gtggcaaaag	acattgacaa	actcgcccag	420
gtggaaaaag	amcamctcct	ggargtgctn	gccgtcctc	gtcmgttggt	ggcagcgctw	480
tccttttgac	acacaaacaa	gttaaaggca	ttttcagccc	ccagaaantt	gtcatcatcc	540
aagatntcgc	acagcactna	tccagttggg	attaat			577

<210> 187
 <211> 534
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(534)
 <223> n = A,T,C or G

<400> 187						
aacatcttcc	tgtataatgc	tgtgtaatat	cgatccgatn	ttgtctgstg	agaatycatw	60
actkggaaaa	gmaacattaa	agcctggaca	ctggtattaa	aattcacaat	atgcaacact	120
ttaaacagt	tgtcaatctg	ctcccyynac	tttgtcatca	ccagtctggg	aakaagggt	180
tgccctattc	acacctgtta	aaaggggcgt	aagcattttt	gattcaacat	cttttttttt	240
gacacaagtc	cgaaaaaagc	aaaagtaaac	agttatyaat	ttgttagcca	attcactttc	300
ttcatgggac	agagccatyt	gatttaaaaa	gcaaattgca	taatattgag	cttygggagc	360
tgatatttga	gcggaagagt	agccttttcta	cttcaccaga	cacaactccc	tttcatattg	420
ggatgttnac	naaagtwaatg	tctctwacag	atgggatgct	tttgtggcaa	ttctgttctg	480
aggatctccc	agtttatitta	ccacttgcac	aagaaggcgt	tttcttcctc	agge	534

<210> 188
 <211> 761
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(761)
 <223> n = A,T,C or G

<400> 188						
agaaaccagt	atctctnaaa	acaacctctc	ataccttgtg	gacctaat	ttgtgtgcgtg	60
tgtgtgtg	cgcatattat	atagacaggc	acatcttttt	tacttttgta	aaagcttatg	120
cctcttttgg	atctatatct	gtgaaagttt	taatgatctg	ccataatgtc	ttggggacct	180
ttgtcttctg	tgtaaatgg	actagagaaa	acacctatnt	tatgagtcaa	tctagttngt	240
tttattcgac	atgaaggaaa	tttccagatn	acaacactna	caaactctcc	ctkgackarg	300
ggggacaaa	aaaagcaaaa	ctgamcataa	raaacaatwa	cctgggtgaga	arttgcataa	360
acagaaatwr	ggtagtatat	tgaarnacag	catcattaaa	rmgttwtktt	wttctccctt	420
gcaaaaaaca	tgtacngact	tcccgttgag	taatgccaag	ttgttttttt	tatnataaaa	480
cttgcccttc	attacatggt	tnaaagtgg	gtgggtggcc	aaaatattga	aatgatggaa	540
ctgactgata	aagctgtaca	aataagcagt	gtgcctaaca	agcaacacag	taatgttgac	600
atgcttaatt	cacaaatgct	aatttcatta	taaatgtttg	ctaaaataca	ctttgaacta	660
tttttctgt	ttcccagagc	tgagatntta	gattttatgt	agtatnaagt	gaaaaantac	720
gaaaataata	acattgaaga	aaaananaaa	aaanaaaaaa	a		761

<210> 189
 <211> 482

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(482)
<223> n = A,T,C or G

<400> 189
 tttttttttt tttgccgatn ctactatattt attgcaggan gtgggggtgt atgcaccgca 60
 caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca 120
 aagccgcctg ctgccttctc tgtctgtctc ctgggtgcagg cacatgggga gaccttcccc 180
 aaggcagggg ccaccagtcc aggggtggga atacagggg tgggagtgt gcataagaag 240
 tgataggcac aggccacccg gtacagaccc ctcggtcct gacaggtnga tttcgaccag 300
 gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc 360
 aaatttggtc ngtcatngaa ngggcanttt tccaantng gctnggtctt ggtaaccttg 420
 gttcggccca gctccncgtc caaaaantat tcaccnct ccnaattgt tgcnggnccc 480
 cc 482

<210> 190
<211> 471
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(471)
<223> n = A,T,C or G

<400> 190
 tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg 60
 aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtntctca 120
 aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag 180
 cgcttttgac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt 240
 taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt 300
 tgaaaaattt catgtatgca atccaaccaa agaacttnat tggatgatcat gantnctcta 360
 ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacncngt acaaaaanaa 420
 tctgtaattn anttcaacct ccgtacngaa aaatnttntt tatacactcc c 471

<210> 191
<211> 402
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(402)
<223> n = A,T,C or G

<400> 191
 gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct 60
 gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa 120
 attcttcacc agtcacatct tctaggacct ttttggtatc agttagtata agctcttcca 180
 cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg 240
 ctggttctct aacaatgtcc tctccttgaa gtatttggt gaacaacca cctaaagtcc 300
 ctttgtgcac ccatttttaa tatacttaat agggcattgk tncactaggt taaattctgc 360
 aagagtcac tgtctgcaaa agttgcgtta gtatatctgc ca 402

<210> 192
 <211> 601
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(601)
 <223> n = A,T,C or G

<400> 192
 gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60
 ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120
 atgcytyttt gaytaccgtg tgccaagtgc tgggtgattct yaacacacyt ccatcccgtt 180
 cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc 240
 acgagacact tgaaagggtg aacaaagcga ytcttgcat gctttttgtc cctccggcac 300
 cagttgtcaa tactaaccgg ctggtttgcc tccatcacat ttgtgatctg tagctctgga 360
 tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcarg tcttggtgcc 420
 tgttgatcaa ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac 480
 aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag 540
 cctcgatgta gccggccagc gccaaaggcag gcgcctgag cccaccagc agcagaagca 600
 g 601

<210> 193
 <211> 608
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(608)
 <223> n = A,T,C or G

<400> 193
 atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact 60
 ggtcccgtg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt 120
 cccaacgcag gcagmagcgg gcccggtcaa tgaactccay tctgtggttg gggtkgacgg 180
 tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccagc tgtgcgggac 240
 ctgcagcgaa actcctcgat ggtcatgagc ggggaagcga tgaggcccag gcccttgccc 300
 agaaccttcc gcctgttctc tggcgtcacc tgcagctgct gccgctgaca ctgggcctcg 360
 gaccagcgga caaacggcrt tgaacagccg cacctcacgg atgcccagtg tgtcgcgctc 420
 caggammgsc accagcgtgt ccagggtcaat gtcgggtgaag ccctccgagg gtrattggcg 480
 ctgcagtggt tttgtcgatg ttctccaggc acaggctggc cagctgagggt tcatcgaaga 540
 gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggctcg cagttcttct tcagggaactc 600
 cagccaat 608

<210> 194
 <211> 392
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(392)
 <223> n = A,T,C or G

<400> 194
 gaacggctgg accttgccctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt 60

ccagtccgag	cagccccaga	ccgctgccgc	ccgaagctaa	gcctgcctct	ggccttcccc	120
tccgcctcaa	tgcagaacca	gtagtgggag	cactgtgttt	agagttaaga	gtgaacactg	180
tttgatttta	cttggaatt	tcctctgtta	tatagctttt	cccaatgcta	atttccaaac	240
aacaacaaca	aaataacatg	tttgccctgtt	aagttgtata	aaagtaggtg	attctgtatt	300
taaagaaaat	attactgtta	catatactgc	ttgcaatttc	tgtattttatt	gktnctstgg	360
aaataaatat	agttattaaa	ggttgtcant	cc			392

<210> 195
 <211> 502
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(502)
 <223> n = A,T,C or G

<400> 195						
ccsttkgagg	ggtkaggkyc	cagttyccga	gtggaagaaa	caggccagga	gaagtgcgtg	60
ccgagctgag	gcagatgttc	ccacagtgc	ccccagagcc	stgggstata	gtytctgacc	120
cctcncaagg	aaagaccacs	ttctggggac	atgggctgga	gggcaggacc	tagaggcacc	180
aagggaaggg	cccattccgg	ggstgttccc	cgaggaggaa	gggaaggggc	tctgtgtgcc	240
cccagaggg	aagaggccct	gagtcctggg	atcagacacc	ccttcacgtg	tatccccaca	300
caaatgcaag	ctcaccaagg	tcccctctca	gtccccttcc	stacaccctg	amcgggccact	360
gscscacacc	cacccagagc	acgccaccgc	ccatggggar	tgtgctcaag	gartcgcnng	420
gcarcgtgga	catctngtcc	cagaaggggg	cagaatctcc	aatagangga	ctgarcmstt	480
gctnanaaaa	aaaaanaaaa	aa				502

<210> 196
 <211> 665
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(665)
 <223> n = A,T,C or G

<400> 196						
ggttacttgg	tttcattgcc	accacttagt	ggatgtcatt	tagaaccatt	ttgtctgtct	60
cctctggaag	ccttgccgag	agcggacttt	gtaattgttg	gagaataact	gctgaatttt	120
wagctgtttk	gagttgatts	gcaccactgc	accacaact	tcaatatgaa	aacyawttga	180
actwatttat	tatcttgtga	aaagtataac	aatgaaaatt	ttgttcatac	tgtattkatc	240
aagtatgatg	aaaagcaawa	gatatatatt	cttttattat	gttaaattat	gattgccatt	300
attaatcggc	aaaatgtgga	gtgtatgttc	ttttcacagt	aatatatgcc	ttttgtaact	360
tcacttggtt	attttattgt	aaatgartta	caaaattcct	aatttaagar	aatggatgt	420
watatttatt	tcattaat	ctttcctkgt	ttacgtwaat	tttgaaaaga	wtgcatgatt	480
tcttgacaga	aatcgatcct	gatgctgtgg	aagtagtttg	accacatcc	ctatgagttt	540
ttcttagaat	gtataaagg	tgtagcccat	cnaacttcaa	agaaaaaat	gaccacatac	600
tttgcaatca	ggctgaaatg	tggcatgctn	ttctaattcc	aactttataa	actagcaaan	660
aagtg						665

<210> 197
 <211> 492
 <212> DNA
 <213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(492)
 <223> n = A,T,C or G

<400> 197

tttntttttt	ttttttttgc	aggaaggatt	ccattttattg	tggatgcatt	ttcacaatat	60
atgtttattg	gagcgatcca	ttatcagtga	aaagtatcaa	gtgtttataa	natttttagg	120
aaggcagatt	cacagaacat	gctngtcngc	ttgcagtttt	acctcgtana	gatnacagag	180
aattatagtc	naaccagtaa	acnaggaatt	tacttttcaa	aagattaaat	ccaaactgaa	240
caaaattcta	ccctgaaact	tactccatcc	aaatattgga	ataanagtca	gcagtgtatac	300
attctcttct	gaactttaga	ttttctagaa	aaatatgtaa	tagtgatcag	gaagagctct	360
tgttcaaaag	tacaacnaag	caatgttccc	ttaccatagg	ccttaattca	aactttgatc	420
catttcactc	ccatcacggg	agtcaatgct	acctgggaca	cttgtatttt	gttcatnctg	480
ancntggctt	aa					492

<210> 198
 <211> 478
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(478)
 <223> n = A,T,C or G

<400> 198

tttnttttgn	atttcantct	gtannaanta	ttttcattat	gtttattana	aaaatatnaa	60
tgntccacn	acaaatcatn	ttacntnagt	aagaggccan	ctacattgta	caacatacac	120
tgagtatatt	ttgaaaagga	caagttttaa	gtanacncat	attgccganc	atancacatt	180
tatacatggc	ttgattgata	tttagcacag	canaaactga	gtgagttacc	agaaanaaat	240
natatatgtc	aatcngattt	aagatacaaa	acagatccta	tggtagatan	catcntgtag	300
gagttgtggc	tttatgttta	ctgaaagtca	atgcagttcc	tgtacaaaaga	gatggccgta	360
agcattctag	tacctctact	ccatggttaa	gaatcgtaca	cttatgttta	catatgtnc	420
gggtaagaat	tgtgttaagt	naanttatgg	agaggtccan	gagaaaaatt	tgatncaa	478

<210> 199
 <211> 482
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(482)
 <223> n = A,T,C or G

<400> 199

agtgacttgt	cctccaacaa	aacccttga	tcaagtttgt	ggcactgaca	atcagaccta	60
tgctagttcc	tgatcatctat	tcgctactaa	atgcagactg	gaggggacca	aaaaggggca	120
tcaactccag	ctggattatt	ttggagcctg	caaactctatt	cctacttgta	cggactttga	180
agtgattcag	tttctcttac	ggatgagaga	ctggtctcaag	aatatcctca	tgcagcttta	240
tgaagccnac	tctgaacacg	ctggttatct	nagatgagaa	ncagagaaat	aaagtcnaga	300
aaatttacct	ggangaaaag	aggctttngg	ctggggacca	tccattgaa	ccttctctta	360
anggacttta	agaanaaact	accacatgtn	tgtngtatcc	tggtgccngg	ccgtttantg	420
aacntngacn	ncacccttnt	ggaatanant	cttgacngcn	tcctgaactt	gctcctctgc	480
ga						482

<210> 200
 <211> 270

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<220>
<221> misc_feature
<222> (1)...(270)
<223> n = A,T,C or G
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<400> 200									
cggccgcgaag	tgcaactcca	gctggggccg	tgccgacgaa	gattctgcca	gcagttggtc				60
cgactgcgac	gacggcgggc	gcyacagtgc	caggtgcagc	gcgggcgcc	ggggtcttgc				120
aaggctgagc	tgacgccgca	gaggtcgtgt	cacgctccac	gaccttgacg	cgctcgggga				180
cagccggaac	agagcccgt	gaangcggga	ggcctcgggg	agcccctcgg	gaagggcggc				240
ccqagagata	cgcaggtgca	ggtggccgcc							270

<210> 201
<211> 419
<212> DNA
<213> Homo sapien

```
<220>
<221> misc_feature
<222> (1)...(419)
<223> n = A,T,C or G
```

<400> 201							
tttttttttt	ttttggaatc	tactgcgagc	acagcaggtc	agcaacaagt	ttattttgca		60
gctagcaagg	taacagggtg	gggcatgggt	acatgttcag	gtcaacttcc	tttgtcgtgg		120
ttgattgggt	tgtctttatg	ggggcggggg	ggggtagggg	aaancgaagc	anaantaaca		180
tggagtgggt	gcaccctccc	tgtagaacct	ggttacnaaa	gcttggggca	gttcacctgg		240
tctgtgaccg	tcattttctt	gacatcaatg	ttattagaag	tcaggatatc	ttttagagag		300
tccactgtnt	ctggaggggg	attagggttt	cttgccaana	tccaancaa	atccacntga		360
aaaagttgga	tgatncangt	acngaatacc	ganggcatan	ttctcatant	cggtggcca		419

```
<210> 202
<211> 509
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(509)
<223> n = A,T,C or G
```

<400> 202						
tttntttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tggcacttaa	tccattttta	tttcaaaatg	tctacaaant	ttnaatncnc	cattatacng	120
gtnattttnc	aaaatctaaa	nnttattcaa	atntnagcca	aantccttac	ncaaatnmaa	180
tacncncaaa	aatcaaaaaat	atacntntct	ttcagcaaac	ttngttacat	aaattaaaaa	240
aatatatacg	gctggtgttt	tcaaagtaca	attatcttaa	cactgcaaac	atnttttnaa	300
ggaactaaaa	taaaaaaaaa	catnccgcga	aaggttaaag	ggaacaacaa	attcntttta	360
caacancnmc	nattataaaa	atcatatctc	aaatcttagg	ggaatatata	cttcacacng	420
ggaatctaac	ttttactnca	ctttgtttat	ttttttanaa	ccattgtntt	gggcccaaca	480
caatggnaat	nccnccnccn	tggaactagt				509

<210>	203
<211>	583
<212>	DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(583)

<223> n = A,T,C or G

<400> 203

tttttttttt	ttttttttga	ccccctctt	ataaaaaaca	agttaccatt	ttattttact	60
tacacatatt	tattttataa	ttggtattag	atattcaaaa	ggcagctttt	aaaatcaaac	120
taaatggaaa	ctgccttaga	tacataattc	ttaggaatta	gcttaaaatc	tgcttaaagt	180
gaaaatcttc	tctagctctt	ttgactgtaa	atttttgact	cttgtaaaac	atccaaattc	240
atttttcttg	tctttaaaat	tatctaattc	ttccattttt	tccctattcc	aagtcaattt	300
gcttctctag	cctcatttcc	tagctcttat	ctactattag	taagtggctt	ttttcctaaa	360
agggaaaaca	ggaagagana	atggcacaca	aaacaaacat	tttatattca	tatttctacc	420
tacgttaata	aaatagcatt	ttgtgaagcc	agctcaaaag	aaggcttaga	tccttttatg	480
tccattttag	tcactaaacg	atatcnaaag	tgccagaatg	caaaagggtt	gtgaacattt	540
attcaaaaga	taataataaga	tatttcacat	actcatcttt	ctg		583

<210> 204

<211> 589

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(589)

<223> n = A,T,C or G

<400> 204

ttttttttnt	tttttttttt	tttttttctc	ttcttttttt	ttganaatga	ggatcgagtt	60
tttcaactctc	tagatagggc	atgaagaaaa	ctcatctttc	cagcttttaa	ataacaatca	120
aatctcttat	gctatatcat	attttaagtt	aaactaatga	gtcactggct	tatcttctcc	180
tgaaggaaat	ctgttcattc	ttctcattca	tatagtтата	tcaagtacta	ccttgcatat	240
tgagagggtt	ttcttctcta	tttacacata	tatttccatg	tgaatttgta	tcaaaccctt	300
attttcatgc	aaactagaaa	ataatgtntt	cttttgcata	agagaagaga	acaatatnag	360
cattacaaaa	ctgctcaaat	tgtttggtta	gnttatccat	tataattagt	tnggcaggag	420
ctaatacaaa	tcacatttac	ngacnagcaa	taataaaact	gaagtaccag	ttaaatatcc	480
aaaataatta	aaggaacatt	tttagcctgg	gtataattag	ctaattcact	ttacaagcat	540
ttattnagaa	tgaattcaca	tgttattatt	cctnagccca	acacaatgg		589

<210> 205

<211> 545

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(545)

<223> n = A,T,C or G

<400> 205

tttttttttt	ttttttcagt	aataatcaga	acaatattta	tttttatatt	taaaattcat	60
agaaaagtgc	cttacattta	ataaaagttt	gtttctcaaa	gtgatcagag	gaattagata	120
tngtcttgaa	caccaatatt	aatttgagga	aaatacacca	aaatacatta	agtaaattat	180
ttaagatcat	agagcttgta	agtgaaaaga	taaaatttga	cctcagaaac	tctgagcatt	240
aaaaatccac	tatttagcaa	taaattacta	tggtactctt	gctttaattt	tgtgatgaat	300
atgggggtgc	actggtaaac	caacacattc	tgaaggatac	attacttagt	gatagattct	360

tatgtacttt	gctanatnac	gtggatatga	gttgacaagt	ttctctttct	tcaatctttt	420
aaggggcnga	ngaatgagg	aagaaaagaa	aaggattacg	catactgttc	tttctatngg	480
aaggattaga	tatgtttcct	ttgccaatat	taaaaaata	ataatgttta	ctactagtga	540
aaccc						545

<210> 206
 <211> 487
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(487)
 <223> n = A,T,C or G

<400> 206						
tttttttttt	tttttttagtc	aagttttctna	tttttattat	aattaaagtc	ttggtcattt	60
catttattag	ctctgcaact	tacatattta	aattaaagaa	acgttnttag	acaactgtna	120
caatttataa	atgtaagggtg	ccattattga	gtanatata	tcctccaaga	gtggatgtgt	180
cccttctccc	accaactaat	gaancagcaa	cattagttaa	atatttattag	tagatnatac	240
actgctgcaa	acgctaattc	tcttctccat	ccccatgtng	atattgtgta	tatgtgtgag	300
ttggtnagaa	tgcatcanca	atctnacaat	caacagcaag	atgaagctag	gcntgggctt	360
tcggtgaaaa	tagactgtgt	ctgtctgaat	caaagtatct	gacctatcct	cgggtggcaag	420
aactcttcga	accgcttcct	caaaggcngc	tgccacattt	gtggcntctn	ttgcacttgt	480
ttcaaaa						545

<210> 207
 <211> 332
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(332)
 <223> n = A,T,C or G

<400> 207						
tgaattggct	aaaagactgc	atttttanaa	ctagcaactc	ttatttcttt	cctttaaaaa	60
tacatagcat	taaatcccaa	atcctattta	aagacctgac	agcttgagaa	ggtcactact	120
gcatttatag	gcacttctgg	tggttctgct	gttacntttg	aantctgaca	atccttgana	180
atctttgcat	gcagaggagg	taaaagggtat	tggattttca	cagaggaana	acacagcgca	240
gaaatgaagg	ggccaggctt	actgagcttg	tccactggag	ggctcatggg	tgggacatgg	300
aaaagaaggc	agcctaggcc	ctggggagcc	ca			332

<210> 208
 <211> 524
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(524)
 <223> n = A,T,C or G

<400> 208						
agggcgtggg	gcggagggcg	ttactgtttt	gtctcagtaa	caataaatac	aaaaagactg	60
gttggtttcc	ggcccatcc	aaccacgaag	ttgattttctc	ttgtgtgcag	agtgactgat	120
tttaaaggac	atggagcttg	tcacaatgtc	acaatgtcac	agtgtgaagg	gcacactcac	180

tcccgcgtga	ttcacattta	gcaaccaaca	atagctcatg	agtccatact	tgtaaatact	240
tttggcagaa	tacttnttga	aacttgacga	tgataactaa	gatccaagat	atttcccaaa	300
gtaaatagaa	gtgggtcata	atattaatta	cctgttcaca	tcagcttcca	tttacaagtc	360
atgagcccag	acactgacat	caaactaagc	ccacttagac	tcctcaccac	cagtctgtcc	420
tgtcatcaga	caggaggetg	tcaccttgac	caaattctca	ccagtcaatc	atctatccaa	480
aaaccattac	ctgatccact	tccggtaatg	caccaccttg	gtga		524

<210> 209
 <211> 159
 <212> DNA
 <213> Homo sapien

gggtgaggaa	atccagagtt	gccatggaga	aaattccagt	gtcagcattc	ttgtctcttg	60
tggccctctc	ctacactctg	gccagagata	ccacagtcaa	acctggagcc	aaaaaggaca	120
caaaggactc	tcgacccaaa	ctgccccaga	ccctctcca			159

<210> 210
 <211> 256
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(256)
 <223> n = A,T,C or G

actccctggc	agacaaaggc	agaggagaga	gctctgttag	ttctgtgttg	ttgaactgcc	60
actgaatttc	tttccacttg	gactattaca	tgccanttga	gggactaatg	gaaaaacgta	120
tggggagatt	ttanccaatt	tangtntgta	aatggggaga	ctggggcagg	cgggagagat	180
ttgcaggggtg	naaatgggan	ggctgggttg	ttanatgaac	agggacatag	gaggttaggca	240
ccaggatgct	aaatca					256

<210> 211
 <211> 264
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(264)
 <223> n = A,T,C or G

acattgtttt	tttgagataa	agcattgaga	gagctctcct	taacgtgaca	caatggaagg	60
actggaacac	ataccacat	ctttgttctg	agggataatt	ttctgataaa	gtcttgctgt	120
atattcaagc	acatatgtta	tatattattc	agttccatgt	ttatagccta	gttaaggaga	180
ggggagatac	attcngaaag	aggactgaaa	gaaatactca	agtnggaaaa	cagaaaaaga	240
aaaaaaggag	caaatgagaa	gcct				264

<210> 212
 <211> 328
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

<222> (1)...(328)

<223> n = A,T,C or G

<400> 212

acccaaaaat ccaatgctga atatttggt tcattattcc canattcttt gattgtcaaa	60
ggattttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag	120
gtttatataat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccggcag	180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta	240
cccctacnac tctttactct ctgganagg ccagtggtgg tagctataag cttggccaca	300
tttttttttc ctttattcct ttgtcaga	328

<210> 213

<211> 250

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 213

acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt	60
taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct	120
cattatgcca aagganatat acatttcaat tctccaaact tcttctcat tccaagagtt	180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatc tctctnacct	240
tctcatcggt	250

<210> 214

<211> 444

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(444)

<223> n = A,T,C or G

<400> 214

accagaatc caatgctgaa tatttggtt cattattccc agattctttg attgtcaaag	60
gatttaaatg tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg	120
tttatataat cagcaacaat attcaagcgc gacaacagg ttattgaact gcccggcagg	180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac	240
ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat	300
ttttttttcc ttatttcctt tgtcagagat gcgattcatc catatgctan aaaccaacag	360
agtgaacttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt	420
actttgctct ccctaataata cctc	444

<210> 215

<211> 366

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(366)

<223> n = A,T,C or G

<400> 215
 acttatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt 60
 taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct 120
 cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt 180
 ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatata tctctgacct 240
 tctcatcggg aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa 300
 tccaagctgt tttctacact gtaaccaggt ttccaaccaa ggtggaaatc tcctatactt 360
 ggtgcc 366

<210> 216
 <211> 260
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(260)
 <223> n = A,T,C or G

<400> 216
 ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc 60
 caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc atttttttat 120
 taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa 180
 atcaaaaatt tcctnaagtt ntcaagctat catatatact ntatcctgaa aaagcaacat 240
 aattcttctt tccctccttt 260

<210> 217
 <211> 262
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(262)
 <223> n = A,T,C or G

<400> 217
 acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta 60
 tcttgccctat aattttctat tttaataagg aaatagcaaa ttgggggtggg gggaatgtag 120
 ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt 180
 atgaataatc tgtatgatta tatgtctcta gagtagattt ataattagcc acttacccta 240
 atatccttca tgcttgtaaa gt 262

<210> 218
 <211> 205
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(205)
 <223> n = A,T,C or G

<400> 218
 accaaggtgg tgcattaccg gaantggatc aangacacca tcgtggccaa cccctgagca 60
 cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaaagactc 120
 aggctcccc agttctactg acctttgtcc ttangtntna ngtcagggt tgctaggaaa 180
 anaaatcagc agacacaggt gtaaa 205

<210> 219
<211> 114
<212> DNA
<213> Homo sapien

<400> 219
tactgttttg tctcagtaac aataaataca aaaagactgg ttgtgttccg gccccatcca 60
accacgaagt tgattttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga 114

<210> 220
<211> 93
<212> DNA
<213> Homo sapien

<400> 220
actagccagc acaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta 60
aaataagcat ttagtgctca gtcctactg agt 93

<210> 221
<211> 167
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(167)
<223> n = A,T,C or G

<400> 221
actangtgca ggtgcgcaca aatatttgtc gatattccct tcatottgga ttccatgagg 60
tcttttgccc agcctgtggc tctactgtag taagtttctg ctgatgagga gccagnatgc 120
ccccactac cttccctgac gtcceccana aatcacccaa cctctgt 167

<210> 222
<211> 351
<212> DNA
<213> Homo sapien

<400> 222
agggcgtggt gcgaggggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60
gttcttcacc tgtcccccaa tctttaaag gccatactgc ataaagtcaa caacagataa 120
atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180
ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240
taggtgagca tgattagaga gcttgtaggt tgcttttaca tatactctggc atatttgagt 300
ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t 351

<210> 223
<211> 383
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

<400> 223

aaaacaaaca	aacaaaaaaa	acaattcttc	attcagaaaa	attatcttag	ggactgatat	60
tggttaattat	ggtcaattta	atwrrtrttkt	ggggcatttc	cttacattgt	cttgacaaga	120
ttaaaatgtc	tgtgccaaaa	ttttgtattt	tatttgaggaga	cttcttatca	aaagtaatgc	180
tgccaaagga	agtctaaggga	attagtagtg	ttcccmctcac	ttgtttggag	tgtgctattc	240
taaaagattt	tgatttcctg	gaatgacaat	tatatatttaa	ctttgggtggg	ggaaanagtt	300
ataggaccac	agtcttctact	tctgatactt	gtaaattaat	cttttattgc	acttgttttg	360
accattaagc	tatatgttta	aaa				383

<210> 224

<211> 320

<212> DNA

<213> Homo sapien

<400> 224

cccctgaagg	cttcttggtta	gaaaatagta	cagttacaac	caataggaac	aacaaaaaga	60
aaaagtgtgt	gacattgtag	tagggagtgt	gtacccctta	ctcccatca	aaaaaaaaat	120
ggatacatgg	ttaaaggata	raagggcaat	attttatcat	atgttctaaa	agagaaggaa	180
gagaaaatac	tactttctcr	aaatggaagc	ccttaaaggt	gctttgatac	tgaaggacac	240
aaatgtggcc	gtccatcctc	ctttaragtt	gcattgacttg	gacacggtaa	ctgttgagcgt	300
tttaractcm	gcattgtgac					320

<210> 225

<211> 1214

<212> DNA

<213> Homo sapien

<400> 225

gaggactgca	gcccgcactc	gcagccctgg	caggcgccac	tggtcatgga	aaacgaattg	60
ttctgctcgg	gcgtcctggg	gcacccgcag	tgggtgctgt	cagccgcaca	ctgtttccag	120
aactcctaca	ccatcgggct	gggcctgcac	agtcttgagg	ccgaccaaga	gccagggagc	180
cagatgggtg	aggccagcct	ctccgtacgg	caccagaggt	acaacagacc	cttgctcgct	240
aacgacctca	tgctcatcaa	gttgagcgaa	tccgtgtccg	agtctgacac	catccggagc	300
atcagcattg	cttcgcagtg	ccctaccgcg	gggaactctt	gcctcgtttc	tggtgtgggt	360
ctgctggcga	acggcagaat	gcctaccgtg	ctgcagtgcg	tgaacgtgtc	ggtggtgtct	420
gaggaggtct	gcagtaagct	ctatgaccgg	ctgtaccacc	ccagcatgtt	ctgcgcgggc	480
ggagggcaag	accagaagga	ctcctgcaac	ggtgactctg	ggggggccct	gatctgcaac	540
gggtacttgc	agggccttgt	gtctttcgga	aaagcccggt	gtggccaagt	tggcgtgccca	600
ggtgtctaca	ccaacctctg	caaattcact	gagtggtatg	agaaaaccgt	ccaggccagt	660
taactctggg	gactgggaac	ccatgaaatt	gacccccaaa	tacatcctgc	ggaagggaatt	720
caggaatatc	tggtcccagc	ccctcctccc	tcaggcccag	gagtcagggc	ccccagcccc	780
tcctccctca	aaccaagggt	acagatcccc	agccctcctc	ccctcagacc	caggagtcca	840
gacccccag	cccctcctcc	ctcagaccca	ggagtccagc	ccctcctccc	tcagacccag	900
gagtcagac	ccccagccc	ctcctccctc	agaccagggg	gtccaggccc	ccaaccctc	960
ctccctcaga	ctcagagggt	caagccccca	acccctcctt	ccccagaccc	agaggtccag	1020
gtcccagccc	ctcctccctc	agaccagcgg	gtccaatgcc	acctagactc	tcctgttaca	1080
cagtgcctcc	ttgtggcagc	ttgacccaac	cttaccagtt	ggtttttcat	tttttgtccc	1140
tttcccctag	atccagaaat	aaagtctaag	agaagcgcaa	aaaaaaaaaa	aaaaaaaaaa	1200
aaaaaaaaaa	aaaa					1214

<210> 226

<211> 119

<212> DNA

<213> Homo sapien

<400> 226

accagtatg	tgacgggaga	cggaacccca	tgtgacagcc	cactccacca	gggttcccaa	60
agaacctggc	ccagtcataa	tcattcatcc	tgacagtggc	aataatcacg	ataaccagt	119

<210> 227
 <211> 818
 <212> DNA
 <213> Homo sapien

<400> 227
 acaattcata gggacgacca atgaggacag ggaatgaacc cggtctctcc ccagccctga 60
 tttttgctac atatggggtc ctttttcatt ctttgcaaaa acactgggtt ttctgagaac 120
 acggacgggt cttagcacia tttgtgaaat ctgtgtaraa ccgggctttg caggggagat 180
 aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta 240
 gagaaagcca cgctcggcct tctctgaaac aggatggaac ggcagacccc tgaaaacgaa 300
 gcttgctccc ttccaatcag ccacttctga gaacccccat ctaacttcct actggaaaag 360
 agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga 420
 ggaaagggtg caccctcagc agagaagccg agagcttaac tctggctcgt tccagagaca 480
 acctgctggc tgtcttgga tgcgccagc ctttgagagg ccactacccc atgaacttct 540
 gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg 600
 gacaggctct gccctcaagc cggttgaggg cagcaaccac tctcctcccc tttctcacgc 660
 aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggtc 720
 caagaggata tgaggactgt ctacgcctgg ctttgggctg acaccatgca cacacacaag 780
 gtccacttct aggttttcag cctagatggg agtcgtgt 818

<210> 228
 <211> 744
 <212> DNA
 <213> Homo sapien

<400> 228
 actggagaca ctggtgaact tgatcaagac ccagaccacc ccaggtctcc ttctgaggat 60
 gtcatgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagacagtgt 120
 tcgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180
 taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240
 tgctcggtgc acattgggtt gctttgggat aaaagattta tgagccaact attctctggc 300
 accagattct aggccagttt gttccactga agcttttccc acagcagtc acctctgcag 360
 gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt 420
 gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg 480
 ccagacgggtg ttggccactc ccttctaaaa cacaggcgcc ctccctggtga cagtgacccg 540
 ccgtgggatg ccttggccca ttccagcagt ccagttatg catttcaagt ttgggggttg 600
 ttcttttctg taatgttct ctgtgttgtc agctgtcttc atttcttggg ctaagcagca 660
 ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720
 cttcactctg aagtagctgg tgggt 744

<210> 229
 <211> 300
 <212> DNA
 <213> Homo sapien

<400> 229
 cgagtctggg ttttgtctat aaagtttgat ccctcctttt ctcatccaaa tcatgtgaac 60
 cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc 120
 tgcagggttg ttgtttttta attattattg ttagaaacgt caccacagc ccctgttaat 180
 ttgtatgtga cagccaactc tgagaaggct ctatttttcc acctgcagag gatccagtct 240
 cactaggctc ctcttgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 230

cagcagaaca	aatacaaata	tgaagagtgc	aaagatctca	taaaatctat	gctgaggaat	60
gagcgacagt	tcaaggagga	gaagcttgca	gagcagctca	agcaagctga	ggagctcagg	120
caatataaag	tcctgggttc	cactcaggaa	cgagagctga	cccagttaag	ggagaagttg	180
cggaaggga	gagatgcctc	cctctcattg	aatgagcatc	tccaggccct	cctcactccg	240
gatgaaccgg	acaagtccca	ggggcaggac	ctccaagaaa	cagacctcgg	ccgcgaccac	300
g						301

<210> 231

<211> 301

<212> DNA

<213> Homo sapien

<400> 231

gcaagtacgc	tggcaaactct	ctgtcaggtc	agctccagag	aagccattag	tcatttttagc	60
caggaactcc	aagtccacat	ccttggcaac	tggggacttg	cgcaggttag	ccttgaggat	120
ggcaacacgg	gacttctcat	caggaagtgg	gatgtagatg	agctgatcaa	gacggccagg	180
tctgaggatg	gcaggatcaa	tgatgtcagg	ccggttggtg	ccgccaatga	tgaacacatt	240
tttttttgtg	gacatgccat	ccatttctgt	caggatctgg	ttgatgactc	ggtcagcagc	300
c						301

<210> 232

<211> 301

<212> DNA

<213> Homo sapien

<400> 232

agtaggtatt	tcgtgagaag	ttcaacacca	aaactggaac	atagttctcc	ttcaagtgtt	60
ggcgacagcg	gggcttcctg	attctggaat	ataactttgt	gtaaattaac	agccacctat	120
agaagagtcc	atctgctgtg	aaggagagac	agagaactct	gggttcctgc	gtcctgtcca	180
cgtgctgtac	caagtgtctg	tgccagcctg	ttacctgttc	tactgaaaa	tctggctaata	240
gctcttgtgt	atcacttctg	attctgacaa	tcaatcaatc	aatggcctag	agcactgact	300
g						301

<210> 233

<211> 301

<212> DNA

<213> Homo sapien

<400> 233

atgactgact	tcccagtaag	gctctctaag	gggtaagtag	gaggatccac	aggattttgag	60
atgctaaggc	cccagagatc	gtttgatcca	accctcttat	tttcagaggg	gaaaatgggg	120
cctagaagtt	acagagcatc	tagctgggtc	gctggcacc	ctggcctcac	acagactccc	180
gagttagctg	gactacaggc	acacagtcac	tgaagcaggc	cctgttagca	attctatgag	240
tacaaattaa	catgagatga	gtagagactt	tattgagaaa	gcaagagaaa	atcctatcaa	300
c						301

<210> 234

<211> 301

<212> DNA

<213> Homo sapien

<400> 234

aggctctaca	catcgagact	catccatgat	tgatatgaat	ttaaaaatta	caagcaaaga	60
cattttattc	atcatgatgc	tttcttttgt	ttcttctttt	cgttttcttc	tttttctttt	120
tcaatttcag	caacatactt	ctcaatttct	tcaggattta	aaatcttgag	ggattgatct	180
cgctcatga	cagcaagttc	aatgtttttg	ccacctgact	gaaccacttc	caggagtgcc	240
ttgatcacca	gcttaatggg	cagatcatct	gcttcaatgg	cttcgtcagt	atagttcttc	300

t

301

<210> 235
 <211> 283
 <212> DNA
 <213> Homo sapien

<400> 235
 tggggctgtg catcaggcgg gtttgagaaa tattcaattc tcagcagaag ccagaatttg 60
 aattccctca tcttttaggg aatcattttac caggtttgga gaggattcag acagctcagg 120
 tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata 180
 atgttatctt tgaactgatg ctcataaggag agaataataag aactctgagt gatatcaaca 240
 ttagggattc aaagaaatat tagatttaag ctcacactgg tca 283

<210> 236
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 236
 aggtcctcca ccaactgcct gaagcacggt taaaattggg aagaagtata gtgcagcata 60
 aatactttta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg 120
 tcggagcagc atcattaata ccaagcagaa tgcgtaatag ataaatacaa tggatatatag 180
 tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgggttgta 240
 aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc 300
 a. 301

<210> 237
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 237
 cagtggtagt ggtggtggac gtggcggttg tctgtggtgcc ttttttggtg ccggtcacia 60
 actcaatttt tggtcgctcc tttttggcct ttccaattt gtccatctca attttctggg 120
 ccttggtctaa tgcctcatag taggagtcct cagaccagcc atggggatca aacatatcct 180
 ttgggtagtt ggtgccaaagc tctgcaatgg cacagaatgg atcagcttct cgtaaatacta 240
 gggttccgaa attcttttct cctttggata atgtagttca tatccattcc ctcctttatc 300
 t. 301

<210> 238
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 238
 gggcagggtt tttttttttt ttttttgatg gtgcagaccc ttgctttatt tgtctgactt 60
 gttcacagtt cagccccctg ctcagaaaac caacgggcca gctaaggaga ggaggaggca 120
 ccttgagact tccggagtcg aggtctctca ggggtcccca gcccatcaat cattttctgc 180
 accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca 240
 gtgtgggacc cagggtctgt tcttcacagt aggaggtgga agggatgact aatttcttta 300
 t. 301

<210> 239
 <211> 239
 <212> DNA
 <213> Homo sapien

<400> 239

ataagcagct	aggggaattct	ttatttagta	atgtcctaac	ataaaagttc	acataactgc	60
ttctgtcaaa	ccatgatact	gagctttgtg	acaacccaga	aataactaag	agaaggcaaa	120
cataatacct	tagagatcaa	gaaacattta	cacagttcaa	ctgtttaaaa	atagctcaac	180
attcagccag	tgagtagagt	gtgaatgcc	gcatacacag	tatacaggtc	cttcaggga	239

<210> 240

<211> 300

<212> DNA

<213> Homo sapien

<400> 240

ggtcctaag	aagcagcagc	ttccacattt	taacgcaggt	ttacgggtgat	actgtccttt	60
gggatctgcc	ctccagtgg	accttttaag	gaagaagtgg	gcccaagcta	agttccacat	120
gctgggtgag	ccagatgact	tctgttccct	ggtcactttc	ttcaatgggg	cgaatggggg	180
ctgccaggtt	tttaaaatca	tgcttcatct	tgaagcacac	ggtcacttca	ccctcctcac	240
gctgtgggtg	tactttgatg	aaaataccca	ctttgttggc	ctttctgaag	ctataatgtc	300

<210> 241

<211> 301

<212> DNA

<213> Homo sapien

<400> 241

gaggtctggt	gctgaggtct	ctgggctagg	aagaggagtt	ctgtggagct	ggaagccaga	60
cctcttttga	ggaaactcca	gcagctatgt	tggtgtctct	gaggggaatgc	aacaaggctg	120
ctcctccatg	tattggaaaa	ctgcaaactg	gactcaactg	gaaggaagtg	ctgctgccag	180
tgtgaagaac	cagcctgagg	tgacagaaac	ggaagcaaac	aggaacagcc	agtcttttct	240
tcctcctcct	gtcatacggt	ctctctcaag	catcctttgt	tgtcaggggc	ctaaaaggga	300
g						301

<210> 242

<211> 301

<212> DNA

<213> Homo sapien

<400> 242

ccgaggtcct	gggatgcaac	caatcactct	gtttcacgtg	acttttatca	ccatacaatt	60
tgtggcattt	cctcattttc	tacattgtag	aatcaagagt	gtaaataaat	gtatatcgat	120
gtcttcaaga	atatatcatt	cctttttcac	tagaaccat	tcaaaatata	agtcaagaat	180
cttaatatca	acaaatatat	caagcaaact	ggaaggcaga	ataactacca	taatttagta	240
taagtacca	aagttttata	aatcaaaagc	cctaatagata	accattttta	gaattcaatc	300
a						301

<210> 243

<211> 301

<212> DNA

<213> Homo sapien

<400> 243

aggtaagtcc	cagtttgaag	ctcaaaagat	ctggatatgag	catagggtca	tcgacgacat	60
ggtggcccaa	gctatgaaat	cagagggagg	cttcatctgg	gcctgtaaaa	actatgatgg	120
tgacgtgcag	tcggactctg	tggcccaagg	gtatggctct	ctcggcatga	tgaccagcgt	180
gctggtttgt	ccagatggca	agacagtaga	agcagaggct	gccacggga	ctgtaacccg	240
tcactaccgc	atgttccaga	aaggacagga	gacgtccacc	aatccattg	cttccatttt	300
t						301

<210> 244

<211> 300
 <212> DNA
 <213> Homo sapien

<400> 244
 gctgggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacott gaaatggaaa 60
 gtcatgcaat cccattttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120
 ccaggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa 180
 aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ctttcttatt tatgtgaaca 240
 actgtttgtc ttttgtgtat cttttttaa ctgtaaagt caattgtgaa aatgaatattc 300

<210> 245
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 245
 gtctgagtat ttaaaatggt attgaaatta tccccaacca atggttagaaa agaaagaggt 60
 tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120
 aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180
 gttttcaaag agcagagatg caattaaata ttgttttagca tcaaaaaggc cactcaatc 240
 agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa 300
 g 301

<210> 246
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 246
 ggtctgtcct acaatgcctg cttcttgaaa gaagtoggca ctttctagaa tagctaaata 60
 acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata 120
 agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac 180
 taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240
 caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa 300
 c 301

<210> 247
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 247
 aggtcctttg gcagggtcga tggatcagag ctcaaactgg agggaaaggc atttcgggta 60
 gcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttggtt cccccacgct 120
 gtgtcctgtg ttcagggtcg acacacaatc ctcatgggaa caggatcacc catgcgctgc 180
 ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc 240
 cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta 300
 a 301

<210> 248
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 248
 aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact 60
 attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttaagaatt 120

acaggaagaa agtgggttgg aagacagcca aagaaataaa agcagattaa attgtatcag 180
gtacattcca gcctgttggc aactccataa aaacatttca gatttttaatc ccgaatttag 240
ctaagagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc 300
c 301

<210> 249
<211> 301
<212> DNA
<213> Homo sapien

<400> 249
gtccagagga agcacctggg gctgaactag gcttgccctg ctgtgaactt gcacttggag 60
ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgccccgcc 120
ccaggagagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc 180
catcgtaatg aattattttg aaaattaatt ccaaccatcct ttcagattct ggatggaaag 240
actgaatcct tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt 300
a 301

<210> 250
<211> 301
<212> DNA
<213> Homo sapien

<400> 250
ggtctgtgac aaggacttgc aggctgtggg aggcaagtga cccttaacac tacacttctc 60
cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc 120
cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac 180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta 240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc 300
a 301

<210> 251
<211> 301
<212> DNA
<213> Homo sapien

<400> 251
gccgaggtcc tacatttggc ccagtttccc cctgcacacct ctccagggcc cctgcctcat 60
agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat 120
ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct 180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccgaa 240
cctctggagg ggggcagtgg aatcccagct ccaggacgga tctgtctgaa aagatatcct 300
c 301

<210> 252
<211> 301
<212> DNA
<213> Homo sapien

<400> 252
gcaaccaatc actctgtttc acgtgacttt tatcaccata caatttgtgg catttctca 60
ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120
tcatttcctt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa 180
atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt 240
tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc 300
a 301

<210> 253

<211> 301
 <212> DNA
 <213> Homo sapien

<400> 253
 ttccctaaga agatgttatt ttgttgggtt ttgttccccc tccatctcga ttctcgtacc 60
 caactaaaaa aaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct 120
 tggctctgatt gttttcagac cttaaaatat aaacttgttt cacaagcttt aatccatgtg 180
 gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt 240
 tccatagtgc ccacagggtg ttctcacat tttctccata ggaaaatgct ttttccaag 300
 g 301

<210> 254
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 254
 cgctgcgcct ttcccttggg ggaggggcaa ggccagaggg ggtccaagtg cagcacgagg 60
 aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaatcccc 120
 ccaaattctct tcatcttacc ctggtggact cctgactgta gaattttttg gttgaaacaa 180
 gaaaaaataa agcttttggg cttttcaagg ttgcttaaca ggtactgaaa gactggcctc 240
 acttaaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc 300
 t 301

<210> 255
 <211> 302
 <212> DNA
 <213> Homo sapien

<400> 255
 agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgtct tttattataa 60
 attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttgat 120
 tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg 180
 aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta 240
 aacattatta aaaaacaaga aacaacaaa aaaatagaga aaaaaaccac cccaacacac 300
 aa 302

<210> 256
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A, T, C or G

<400> 256
 gttccagaaa acattgaagg tggcttccca aagtctaact agggatacc cctctagcct 60
 aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc 120
 acccccaaaa gcctggacac cttgagcaca cagttatgac caggacagac tcatctctat 180
 aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt 240
 gtggcctctc ggcttgggta gcaagaacat tcagggttag cctaagttan tcgtgttagt 300
 t 301

<210> 257
 <211> 301

<212> DNA

<213> Homo sapien

<400> 257

gttggtggagg aactctggct tgctcattaa gtcctactga ttttcactat cccctgaatt	60
tccccactta tttttgtctt tcaactatcg aggccttaga agaggtctac ctgcctccag	120
tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat	180
gtcacattac tcccttcagt gattttcttg agaagtgcc atccctgaat gccaccaaga	240
tcttaatctt cacatcttta atcttatctc tttgactcct ctttacaccg gagaaggctc	300
c	301

<210> 258

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 258

cagcagtagt agatgccgta tgccagcacg cccagcactc ccaggatcag caccagcacc	60
agggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc	120
cccaggggcaa caagaatcca ataccaggac tggggcaaat cttcaaagat cttaacactg	180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat	240
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac	300
t	301

<210> 259

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 259

tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg	60
gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa	120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggctctgt	180
tccagctcac atctcatctg catgcagcac ggaccggatg cgcccactgg gtcttggtt	240
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcattccttg ctccagggtg	300
c	301

<210> 260

<211> 301

<212> DNA

<213> Homo sapien

<400> 260

ttttttttct ccctaaggaa aaagaaggaa caagtctcat aaaaccaa at aagcaatggt	60
aagggtgtctt aacttgaaaa agattaggag tcaactggtt acaagttata attgaatgaa	120
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaaca caggattaac	180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc	240
actgagacat cagtacctgc ccgggcggcc gctcgagccg aattctgcag atatccatca	300

c

301

<210> 261
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 261
 aaatatttoga gcaaatcctg taactaatgt gtctccataa aaggctttga actcagtga 60
 tctgcttcca tccacgattc tagcaatgac ctctcggaca tcaaagctcc tcttaagggt 120
 agcaccaact attccataca attcatcagc aggaataaaa ggctcttcag aagggtcaat 180
 ggtgacatcc aatttcttct gataatttag attcctcaca accttcctag ttaagtgaag 240
 ggcatgatga tcatccaaag ccagtggtc acttactcca gactttctgc aatgaagatc 300
 a 301

<210> 262
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 262
 gaggagagcc tggtacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc 60
 tgtgagcttc ttgccgaag tctctcagaa atttaaaaag atgcaaatacc ctgagtcacc 120
 cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcaactctgca tttgtaatga 180
 gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgcgc 240
 catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaaagaat 300
 c 301

<210> 263
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 263
 tttagcttgt ggtaaagac tcacaaaact gattttaaaa tcaagttaat gtgaattttg 60
 aaaattacta cttaatccta attcacaata acaatggcat taagggttga cttgagttgg 120
 ttcttagtat tatttatggg aaataggctc ttaccacttg caaataactg gccacatcat 180
 taatgactga cttccagta aggtctctta aggggtaagt angaggatcc acaggatttg 240
 agatgctaag gcccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg 300
 g 301

<210> 264
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 264
 aaagacgtta aaccactcta ctaccacttg tggaactctc aaagggtaaa tgacaaascc 60
 aatgaatgac tctaaaaaca atattttacat ttaatgggtt gtagacaata aaaaaacaag 120
 gtggatagat ctagaattgt aacattttta gaaaaccata scatttgaca gatgagaaag 180
 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240
 acccttcata taaattcact atcttggctt gaggcactcc ataaaatgta tcacgtgcat 300
 a 301

<210> 265
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 265
 tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcatctttgt 60
 cttcttgtga cgcagtatct cttctctggg gagaagccgg gaagtcttct cctggctcta 120
 catattcttg gaagtctcta atcaactttt gtccatttg tttcatttct tcaggaggga 180
 ttttcagttt gtcaacatgt tctctaaca cacttgcca tttctgtaaa gaatccaaag 240
 cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg 300
 c 301

<210> 266
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 266
 taccgtctgc ctttctccc atccaggcca tctgcgaatc tacatgggtc ctcctattcg 60
 acaccagatc actctttcct ctaccacag gcttgctatg agcaagagac acaacctcct 120
 ctcttctgtg ttccagcttc ttttctggtt cttcccaccc cttaagttct attcctgggg 180
 atagagacac caatacccat aacctctctc ctaagcctcc ttataaccca ggggtgcacag 240
 cacagactcc tgacaactgg taaggccaat gaactgggag ctcacagctg gctgtgcctg 300
 a 301

<210> 267
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 267
 aaagagcaca ggccagctca gcctgccctg gccatctaga ctcagcctgg ctccatgggg 60
 gttctcagtg ctgagtcctat ccaggaaaag ctcacctaga cttcttgagg ctgaatcttc 120
 atcctcacag gcagcttctg agagcctgat attcctagcc ttgatgggtc ggagtaaagc 180
 ctcattctga ttcctctcct tcttttcttt caagttggct ttctcacat ccctctgttc 240
 aattcgcttc agcttgctctg ctttagccct catttcaga agcttcttct ctttggcatc 300
 t 301

<210> 268
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 268
 aatgtctcac tcaactactt ccagcctac cgtggcctaa ttctgggagt tttcttctta 60
 gatcttggga gagctggttc ttctaaggag aaggaggaag gacagatgta actttggatc 120
 tcgaagagga agtctaattg aagtaattag tcaacgggtc ttgtttagac tcttgggaata 180
 tgctgggttg ctcaagtgc ctttttggag aaagcaagta ttattcttaa ggagtaacca 240
 cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact 300
 a 301

<210> 269
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 269
 taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat 60
 aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact 120
 atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta 180
 cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta 240
 tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc 300
 t 301

<210> 270
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 270
 cattgaagag cttttgcgaa acatcagaac acaagtgcct ataaaattaa ttaagcctta 60
 cacaagaata catattcctt ttattttctaa ggagttaaac atagatgtag ctgatgtgga 120
 gagcttgctg gtgcagtgc aattggataa cactattcat ggccgaattg atcaagtcaa 180
 ccaactcctt gaactggatc atcagaagaa ggggtggcg ccatatactg cactagataa 240
 tggaccaacc aactaaattc totcaccagg ctgtatcagt aaactggctt aacagaaaac 300
 a 301

<210> 271
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 271
 aaaaggttct cataagatta acaatttaaa taaatatttg atagaacatt cttttctcatt 60
 tttatagctc atcttttagg ttgatattca gttcatgctt cccttgctgt tcttgatcca 120
 gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt ggggtccaagg 180
 tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt 240
 tctctcctcc agatganaac tgatcatgag ccacattttt ggggttttata gaagcagtca 300
 c 301

<210> 272
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 272
 taaattgcta agccacagat aacaccaatc aatggaaca aatcactgtc ttcaaagtgc 60
 ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga 120
 tccaataatt ccctcatgat gagcaagaaa aattccttgc gcaccctcc tgcattccaca 180
 gcatcttctc caacaaatat aaccttgagt ggcttctgt aatctatgtt ctttgttttc 240
 ctaaggactt ccattgcac tcctacaata ttttctctac gcaccactag aattaagcag 300
 g 301

<210> 273
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 273

acatgtgtgt atgtgtatct ttgggaaan aanaagacat cttgtttayt atttttttgg	60
agagangctg ggacatggat aatcacwtaa ttgtctayta tyactttaat ctgactygaa	120
gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc	180
ttytttctgt ccagagagag tatcagtgc ananatttma gggatgaamac atgmattggg	240
gggacttnty ttacngagm accctgccc sgccgctcg makcngantt ccgcsananc	300
t	301

<210> 274
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 274

cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttcttttgagg	60
aacagtaaatt gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa	120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttggt gaaaagcca	180
tctaggtatg gttgcattct cgtcttctt tctgcagtag ataatgaggt aaccgaaggc	240
aattgtgctt cttttgataa gaagctttct tggatcatatc aggaaattcc aganaaaagtc	300
c	301

<210> 275
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 275

tccgtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg	60
gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc	120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtgag	180
tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc	240
agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat	300
a	301

<210> 276
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 276

tgtacacata ctcaataaat aatgactgc attgtggtat tattactata ctgattatat	60
ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatcaaaat	120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc	180
caatacattt aaacatttgg gaaatgaggg ggacaaaatgg aagccagatc aaatttgtgt	240

aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggtcttcctt caatggggat 300
g 301

<210> 277
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 277
tttgttgatg tcagtattttt attacttgcg ttatgagtgc tcacctggga aattctaaag 60
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg 120
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgccccca ccctcgtcct 180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga 240
gttcnctgtc gattacatct gaccagtctc ctttttccga agtcctntccg ttcaatcttg 300
c 301

<210> 278
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 278
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat 60
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca 120
cagtctctac tgttattatg cattacctgg gaatttatat aagcccttaa taataatgcc 180
aatgaacatc tcatgtgtgc tcacaatgtt ctgggactat tataagtgtc tcacaggttt 240
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt 300
c 301

<210> 279
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 279
aaagcaggaa tgacaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact 60
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc 120
ttagaccttt accttcagc caccacacag tgcttgatat ttcagagtca gtcattgggt 180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac 240
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag 300
a 301

<210> 280

<211> 301
 <212> DNA
 <213> Homo sapien

<400> 280
 ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg 60
 tagaaagggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct 120
 tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg 180
 gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga 240
 cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag 300
 t 301

<210> 281
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 281
 aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc 60
 gccgagcaat ccaaattcctg aatgaagggg catcttctga aaaaggagat ctgaatctca 120
 atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa 180
 tgtgtagcac actgcgatta cagctaaata acccgatttt gtgtgtcatg tttgcatttc 240
 tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc 300
 g 301

<210> 282
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 282
 caggctactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60
 tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga 120
 agcgagagaag caaagcccag gcagaacat gctaacctta cagctcagcc tgcacagaag 180
 cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg 240
 cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag 300
 a 301

<210> 283
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 283
 atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag 60
 cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca 120
 gtgcactccc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc 180
 acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcattcttta 240
 ggaaacatat acatttttta aaatctattt tatgtaagaa ctgacagacg aatttgcttt 300
 g 301

<210> 284
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 284
 caggtaaaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt 60

a

<220>

$\langle 222 \rangle$ (1) ... (301)

$\langle 223 \rangle$ n = A, T, C o

11

acatcaccatt	gatcggtacc	cccacccatt	atacgttgta	tgtttacata	aatactcttc	60
aatgatcatt	agtgttttaa	aaaaaatact	gaaaactcct	tctgcatccc	aatctctaac	120
caggaaagca	aatgctat	acagacctgc	aagccctccc	tcaaacnaaa	ctatttctgg	180
attaaatatg	tctgacttct	tttgaggtca	cacgactagg	caaagtgtat	ttacgatctg	240
caaaagctgt	ttgaagagtc	aaagccccc	tgtgaacacg	atttctggac	cctgtaacag	300
t						301

t

<400> 286

十

<400> 287

t

<400> 288

gtacaccta aa ctgcaaggac agctgaggaa tghtaatgggc agccgcgtttt aaagaagtag 60
agtcaataag ctagacaaatt ccagttccag ctcaagtctgg gtatctgcaa agctgcaaaa 120

```

gatcttttaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatatc 180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag 240
tctgccttaa ttttgatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa 300
a 301

```

```

<210> 289
<211> 301
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

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<400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgtctc tggaaactta 60
gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg 120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa 180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaaga 240
tgtgttttgt tttggactct ctgtgtcccc ttccaatgct gtgggtttcc aaccagnnga 300
a 301

```

```

<210> 290
<211> 301
<212> DNA
<213> Homo sapien

```

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<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

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<400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac 60
tgactgatct gttcatttct ctcacagctc ttaccccaa aagcttttcc accctaagt 120
ttctgacctc cttttctaata cacagtaggg atagaggcag anccacctac aatgaacatg 180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc 240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtga 300
a 301

```

```

<210> 291
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttggttgaa acataacaac 60
tatatcagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc 120
tttactcttt tgtttatagg tgaatcacia aatgtatttt tatgtattct gtagttcaat 180
agccatggct gtttacttca ttttaatttat ttagcataaa gacattatga aaaggcctaa 240
acatgagctt cacttcccca ctaactaatt agcatctgtt atttcttaac cgtaatgcct 300
a 301

```

```

<210> 292
<211> 301
<212> DNA
<213> Homo sapien

```

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 292
 accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc 60
 tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttgggtattc 120
 aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg 180
 ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc 240
 tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa 300
 a 301

<210> 293
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 293
 ggtaccaagt gctgggtgcca gcctgttacc tgtttctcact gaaaagtctg gctaagtctc 60
 ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt 120
 aacacaaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgtttctgt 180
 gtgagaattt tttaaaaggc tactttgtata ataacccttg tcattttttaa tgtacctcgg 240
 ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat 300
 g 301

<210> 294
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 294
 tgacccataa caatatacac tagctatctt ttttaactgtc catcattagc accaatgaag 60
 attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag 120
 ttttaactata gtcacaganc ttaaattatc acattgtttt ctatgtctac tgaaaataag 180
 ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc 240
 cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt 300
 t 301

<210> 295
 <211> 305
 <212> DNA
 <213> Homo sapien

<400> 295
 gtactctttc tctccccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta 60
 cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa gtgtctttgt ttaaaattac 120
 ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga 180
 actggtagaa aaacrtctga agagctagtc tatcagcatc tgacagggtga attggatggt 240
 totcagaacc atttcaccca gacagcctgt ttctatcctg ttttaataaat tagtttggtg 300
 tctct 305

<210> 296
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 296
 aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct 60
 cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg 120
 attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac 180
 tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt 240
 tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg 300
 c 301

<210> 297
 <211> 300
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(300)
 <223> n = A,T,C or G

<400> 297
 actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta 60
 aaggttttga aaaccttgaa ggagaatcat ttgacaaga agtacttaag agtctagaga 120
 acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt 180
 tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggtc 240
 accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg 300

<210> 298
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 298
 tatggggttt gtcacccaaa agctgatgct gagaaaggcc tccctggggc ccctcccgcg 60
 ggcattctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgcccggctg 120
 tgaagctctc agatcaatca cgggaagggc ctggcggttg tggccacctg gaaccaccct 180
 gtccctgtctg ttacatttc actaycaggt tttctctggg cattacnatt tgttccccta 240
 caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctccagcgagg 300
 t 301

<210> 299
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 299
 gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggctctctgc 60
 tcactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct cccaggtagc 120
 tgggattgca ggtcacgcc accataccca gctaattttt ttgtattttt agtagagacg 180
 gagtttcgcc atgttggcca gctgggtctca aactcctgac ctcaagcgac ctgcctgcct 240

cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt 300
t 301

<210> 300
<211> 301
<212> DNA
<213> Homo sapien

<400> 300
attcagtttt atttgctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga 60
tatgtcccac acccactggg aaaggctccc acctggctac ttcctctatc agctgggtca 120
gctgcattcc acaaggttct cagcctaatt agtttacta cctgccagtc tcaaaactta 180
gtaaagcaag accatgacat tccccacgg aaatcagagt ttgcccacc gtcttggtac 240
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccagcgc catcccccat 300
g 301

<210> 301
<211> 301
<212> DNA
<213> Homo sapien

<400> 301
ttaaattttt gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagtctgc 60
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt 120
gggaactcac aaagaccctc agagctgaga caccacaac agtgggagct cacaaagacc 180
ctcagagctg agacaccac aacagtggga gctcacaag accctcagag ctgagacacc 240
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt 300
t 301

<210> 302
<211> 301
<212> DNA
<213> Homo sapien

<400> 302
aggtagacat ttagcttctg gtaaatgact cacaaaactg attttaaaat caagttaatg 60
tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac 120
ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg 180
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 240
caggatttga gatgctaagg cccagagat cgtttgatcc aaccctotta ttttcagagg 300
g 301

<210> 303
<211> 301
<212> DNA
<213> Homo sapien

<400> 303
aggtagcaac tgtggaaata ggtagaggat ctttttttct ttccatatca actaagttgt 60
atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac 120
tggctaattg aactaccgct tgcatgttaa aaatgggtgt ttgtgaaatg atcataggcc 180
agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc 240
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300
c 301

<210> 304
<211> 301
<212> DNA

<213> Homo sapien

<400> 304

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acatggatgt tattttgcag actgtcaacc tgaatttgta tttgcttgac attgcctaata 60
tattagtttc agtttcagct taccactttt ttgtctgcaa catgcaraas agacagtgcc 120
cttttttagtg tatcatatca ggaatcatct cacattgggt tgtgccatta ctgggtgcagt 180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga 240
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct 300
c 301

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<210> 305

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (301)

<223> n = A,T,C or G

<400> 305

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gangtacagc gtgggtcaagg taacaagaag aaaaaaatgt gagtggcatc ctgggatgag 60
caggggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggag 120
taaaggagga gaaacagata caaaatctcc aactcagtat taaggatttc tcatgcctag 180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa 240
ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag 300
a 301

```

<210> 306

<211> 8

<212> PRT

<213> Homo sapien

<400> 306

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Val Leu Gly Trp Val Ala Glu Leu
1 5

```

<210> 307

<211> 637

<212> DNA

<213> Homo sapien

<400> 307

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acagggratg aagggaaagg gagaggatga ggaagccccc ctggggattt ggtttggtcc 60
ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatocagaa ataggggcac 120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt 180
cacaccattg gtgaggagg gattaccacc ctgggggtat gaagatgggt gaacacccca 240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga 300
gcaggaggac gcttgacac catgcaggat gacatggggg atgcgctcgg gattggtgtg 360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga 420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtga 480
actcattagg ctgagaacct tgtggaatgc acttgaccga sctgatagag gaagtagcca 540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg 600
ttacagatac tggggcagca aataaaaactg aatcttg 637

```

<210> 308

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(647)

<223> n = A,T,C or G

<400> 308

acgattttca	ttatcatgta	aatcgggtca	ctcaaggggc	caaccacagc	tgggagccac	60
tgctcagggg	aaggttcata	tgggactttc	tactgcccac	ggttctatac	aggatataaa	120
ggngcctcac	agtatagatc	tggtagcaaa	gaagaagaaa	caaacactga	tctctttctg	180
ccacccctct	gacccttttg	aactcctctg	accctttaga	acaagcctac	ctaatactctg	240
ctagagaaaa	gaccaacaac	ggcctcaaag	gatctcttac	catgaaggtc	tcagctaatt	300
cttgggtaag	atgtgggttc	cacattaggt	tctgaatatg	gggggaaggg	tcaatttgct	360
catttttgtt	gtggataaaag	tcaggatgcc	cagggggccag	agcagggggc	tgcttgcttt	420
gggaacaatg	gctgagcata	taaccatagg	ttatggggaa	caaaacaaca	tcaaagtcac	480
tgtatcaatt	gccatgaaga	cttgagggac	ctgaatctac	cgattcatct	taaggcagca	540
ggaccagttt	gagtggcaac	aatgcagcag	cagaatcaat	ggaaacaaca	gaatgattgc	600
aatgtccttt	ttttctcct	gcttctgact	tgataaaagg	ggaccgt		647

<210> 309

<211> 460

<212> DNA

<213> Homo sapien

<400> 309

actttatagt	ttaggctgga	cattggaaaa	aaaaaaaaagc	cagaacaaca	tgtgatagat	60
aatatgattg	gctgcacact	tccagactga	tgaatgatga	acgtgatgga	ctattgtatg	120
gagcacatct	tcagcaagag	ggggaaatac	tcattcattt	tggccagcag	ttgtttgatc	180
accaaacatc	atgccagaat	actcagcaaa	ccttcttagc	tcttgagaag	tcaaagtcag	240
ggggaattta	ttcctggcaa	ttttaatttg	actccttatg	tgagagcagc	ggctaccagc	300
ctgggggtgt	ggagcgaacc	cgtcactagt	ggacatgcag	tggcagagct	cctggtaacc	360
acctagagga	atacacaggc	acatgtgtga	tgccaagcgt	gacacctgta	gcactcaaat	420
ttgtcttgtt	tttgtctttc	ggtgtgtaag	attcttaagt			460

<210> 310

<211> 539

<212> DNA

<213> Homo sapien

<400> 310

acgggactta	tcaaataaag	ataggaaaag	aagaaaactc	aaatattata	ggcagaaatg	60
ctaaagggtt	taaaatatgt	caggattgga	agaaggcatg	gataaagaac	aaagttcagt	120
taggaaagag	aaacacagaa	ggaagagaca	caataaaagt	cattatgtat	tctgtgagaa	180
gtcagacagt	aagatttgtg	ggaaatgggt	tggtttggtg	tatggtatgt	attttagcaa	240
taatctttat	ggcagagaaa	gctaaaatcc	tttagcttgc	gtgaatgatc	acttgctgaa	300
ttcctcaagg	taggcatgat	gaaggagggt	ttagaggaga	cacagacaca	atgaactgac	360
ctagatagaa	agccttagta	tactcagcta	ggaatagtga	ttctgagggc	acactgtgac	420
atgattatgt	cattacatgt	atggtagtga	tggggatgat	aggaaggaag	aacttatggc	480
atattttcac	ccccacaaa	gtcagttaaa	tattgggaca	ctaaccatcc	aggtcaaga	539

<210> 311

<211> 526

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)... (526)

<223> n = A,T,C or G

<400> 311

caaatttgag	ccaatgacat	agaattttac	aaatcaagaa	gcttattctg	gggccatttc	60
ttttgacgtt	ttctctaaac	tactaaagag	gcattaatga	tccataaatt	atattatcta	120
catttacagc	atttaaaatg	tggtcagcat	gaaatattag	ctacagggga	agctaaataa	180
attaaacatg	gaataaagat	ttgtccttaa	atataatcta	caagaagact	ttgatatttg	240
tttttcacaa	gtgaagcatt	cttataaagt	gtcataacct	ttttggggaa	actatgggaa	300
aaaatgggga	aactctgaag	ggttttaagt	atcttacctg	aagctacaga	ctccataacc	360
tctctttaca	gggagctcct	gcagccccta	cagaaatgag	tggttgagat	tcttgattgc	420
acagcaagag	cttctcatct	aaaccctttc	cctttttagt	atctgtgtat	caagtataaa	480
agttctataa	actgtagtnt	acttatttta	atccccaaag	cacagt		526

<210> 312

<211> 500

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)... (500)

<223> n = A,T,C or G

<400> 312

cctctctctc	cccaccccct	gactctagag	aactggggtt	tctcccagta	ctccagcaat	60
tcattttctga	aagcagttga	gccactttat	tccaaagtac	actgcagatg	ttcaaactct	120
ccattttctct	ttcccttcca	cctgccagtt	ttgctgactc	tcaacttgct	atgagtgtaa	180
gcattaagga	cattatgctt	cttcgattct	gaagacaggc	cctgctcatg	gatgactctg	240
gcttcttagg	aaaatatttt	tcttccaaaa	tcagtaggaa	atctaaactt	atccccctct	300
tgacagtgct	tagcagcttc	agacatttgg	ttaagaaccc	atgggaaaaa	aaaaaatcct	360
tgctaagtgt	gtttcctttg	ttaaccanga	ttcttatttg	nctggtatag	aatatcagct	420
ctgaacgtgt	ggtaaagatt	tttgtgtttg	aatataggag	aaatcagttt	gctgaaaagt	480
tagtcttaat	tatctattgg					500

<210> 313

<211> 718

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)... (718)

<223> n = A,T,C or G

<400> 313

ggagatttgt	gtggtttgca	gccgagggag	accaggaaga	tctgcatggt	gggaaggacc	60
tgatgatata	gaggtgagaa	ataagaaagg	ctgctgactt	taccatctga	ggccacacat	120
ctgctgaaat	ggagataatt	aacatcacta	gaaacagcaa	gatgacaata	taatgtctaa	180
gtagtgacat	gtttttgcac	atttccagcc	cttttaataa	tccacacaca	caggaagcac	240
aaaaggaagc	acagagatcc	ctgggagaaa	tgccccggcg	ccatcttggt	tcacgatga	300
gcctcgccct	gtgcctgntc	ccgcttggtg	gggaaggaca	ttagaaaaat	aattgatgtg	360
ttccttaaag	gatggcagga	aaacagatcc	tggtgtggat	atttatttga	acgggattac	420
agatttgaaa	tgaagtcaca	aagtgcagcat	taccaatgag	aggaaaacag	acgagaaaat	480
cttgatgggt	cacaagacat	gcaacaaaca	aaatgggaata	ctgtgatgac	acgagcagcc	540
aactggggag	gagataccac	ggggcagagg	tcaggattct	ggccctgctg	cctaactgtg	600
cgttatacca	atcatttcta	tttctaccct	caaacaagct	gtngaataac	tgacttacgg	660
ttcttntggc	ccacattttc	atnatccacc	ccntcntttt	aannttantc	caaantgt	718

<210> 314
 <211> 358
 <212> DNA
 <213> Homo sapien

<400> 314
 gtttattttac attacagaaa aaacatcaag acaatgtata ctatttcaaa tatatccata 60
 cataatcaaa tatagctgta gtacatgttt tcattgggtgt agattaccac aaatgcaagg 120
 caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa 180
 gctctcggta gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc 240
 ttgttgatt gctgaactgt agtgccctgt attttgett tgtctgtgaa ttctgttgct 300
 tctggggcat ttccttgta tgcagaggac caccacacag atgacagaa tctgaatt 358

<210> 315
 <211> 341
 <212> DNA
 <213> Homo sapien

<400> 315
 taccacctcc ccgctggcac tgatgagccg catcaccatg gtcaccagca ccatgaaggc 60
 ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcgagt 120
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 tagcttctgc tgtaagaggg tggtgtcccg ggggctcgtg cggttattgg tctctgggctt 300
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<210> 316
 <211> 151
 <212> DNA
 <213> Homo sapien

<400> 316
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 cattcagga gctctggttg caatattagt t 151

<210> 317
 <211> 151
 <212> DNA
 <213> Homo sapien

<400> 317
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 ccagggctct gttcttgcca cactgcttg a 151

<210> 318
 <211> 151
 <212> DNA
 <213> Homo sapien

<400> 318
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 gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg 120
 tgggggcggg ttatcaggca gtgataaaca t 151

<210> 319

<211> 151
 <212> DNA
 <213> Homo sapien

<400> 319
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 taagattggg tttatgtgat tttagtgggt a 151

<210> 320
 <211> 150
 <212> DNA
 <213> Homo sapien

<400> 320
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 gagcggtgc cttttttttt tttttttttg ggggggaatt tttttttttt aatagttatt 120
 gagtgttcta cagcttacag taaataccat 150

<210> 321
 <211> 151
 <212> DNA
 <213> Homo sapien

<400> 321
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 tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120
 tgctctgag aatcaaagt cttcatacac t 151

<210> 322
 <211> 151
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(151)
 <223> n = A,T,C or G

<400> 322
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 ttggtggcttg gtcagtttgc cacagggctt ggagatgggt acagtcttct ggcattcggc 120
 attgtgcagg gctcgttca nacttcagtt 151

<210> 323
 <211> 151
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(151)
 <223> n = A,T,C or G

<400> 323
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 nagactcant tactaccag tttgtggttt twtgggagaa atgtaactgg acagttagct 120
 gttcaatyaa aaagacactt ancccatgtg g 151

<210> 324
 <211> 461
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(461)
 <223> n = A, T, C or G

<400> 324
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 agagttacta cgaatcccat cttgggtcca gctatatcac tgacagcatg gtagaagact 180
 gcgaacctca cttctagact ttcacggtgg gacgaaacgg gtccagaaac tgccaggggc 240
 ctcatacagg gatatacaaaa taccctttgt gctaccagg ccctggggaa tcaggtgact 300
 cacacaaatg caatagttgg tcaactgcatt tttaccctgaa ccaaagctaa acccggtgtt 360
 gccacatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga 420
 aaaaacgcac aagagccct gccctgccct agctgangca c 461

<210> 325
 <211> 400
 <212> DNA
 <213> Homo sapien

<400> 325
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<210> 326
 <211> 1215
 <212> DNA
 <213> Homo sapien

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 ccagatggtg gaggccagcc tctccgtacg gcacccagag tacaacagac ccttgctcgc 240
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 aaaaaaaaaa aaaaaa 1215

<210> 327
 <211> 220
 <212> PRT
 <213> Homo sapien

<400> 327
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 Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
 20 25 30
 Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
 35 40 45
 Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
 50 55 60
 Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
 65 70 75 80
 Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
 85 90 95
 Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
 100 105 110
 Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
 115 120 125
 Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
 130 135 140
 Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
 145 150 155 160
 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
 165 170 175
 Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
 180 185 190
 Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
 195 200 205
 Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 210 215 220

<210> 328
 <211> 234
 <212> DNA
 <213> Homo sapien

<400> 328
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 atccgcagtg ggtgctgtca gccacacact gtttcagaa ctctacacc atcgggctgg 180
 gcctgcacag tcttgaggcc gaccaagagc caggagacca gatggtggag gcc 234

<210> 329
 <211> 77
 <212> PRT
 <213> Homo sapien

<400> 329
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105

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20	25	30	
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr			
35	40	45	
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu			
50	55	60	
Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala			
65	70	75	

<210> 330
 <211> 70
 <212> DNA
 <213> Homo sapien

<400> 330
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 gctgcagcca 70

<210> 331
 <211> 22
 <212> PRT
 <213> Homo sapien

<400> 331
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 Val Ser Gly Ser Cys Ser
 20

<210> 332
 <211> 2507
 <212> DNA
 <213> Homo sapien

<400> 332
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<210> 333

<211> 3030

<212> DNA

<213> Homo sapien

<400> 333

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<210> 334

<211> 2417

<212> DNA

<213> Homo sapien

<400> 334

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<210> 335

<211> 2984

<212> DNA

<213> Homo sapien

<400> 335

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<210> 336

<211> 147

<212> PRT

<213> Homo sapien

<400> 336

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Leu	Asp	Ser	Glu	Asn	Thr	Ser	Gly	Ala	Leu	Pro	Arg	Leu	Pro	Gln	Thr
			20					25					30		
Pro	Lys	Gln	Pro	Gln	Lys	Arg	Ser	Arg	Ala	Ala	Phe	Ser	His	Thr	Gln
		35					40					45			
Val	Ile	Glu	Leu	Glu	Arg	Lys	Phe	Ser	His	Gln	Lys	Tyr	Leu	Ser	Ala
	50					55					60				
Pro	Glu	Arg	Ala	His	Leu	Ala	Lys	Asn	Leu	Lys	Leu	Thr	Glu	Thr	Gln
65					70				75						80
Val	Lys	Ile	Trp	Phe	Gln	Asn	Arg	Arg	Tyr	Lys	Thr	Lys	Arg	Lys	Gln
				85					90					95	
Leu	Ser	Ser	Glu	Leu	Gly	Asp	Leu	Glu	Lys	His	Ser	Ser	Leu	Pro	Ala
			100					105					110		
Leu	Lys	Glu	Glu	Ala	Phe	Ser	Arg	Ala	Ser	Leu	Val	Ser	Val	Tyr	Asn
		115					120					125			
Ser	Tyr	Pro	Tyr	Tyr	Pro	Tyr	Leu	Tyr	Cys	Val	Gly	Ser	Trp	Ser	Pro
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Ala	Phe	Trp													
145															

<210> 337

<211> 9

<212> PRT

<213> Homo sapien

<400> 337

Ala	Leu	Thr	Gly	Phe	Thr	Phe	Ser	Ala
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<210> 338

<211> 9

<212> PRT

<213> Homo sapien

<400> 338

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<210> 339

<211> 318

<212> PRT

<213> Homo sapien

<400> 339

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Cys Thr Ser Thr Val Gln Leu Pro Gly Lys Val Val Val Val Thr Gly
      35      40      45
Ala Asn Thr Gly Ile Gly Lys Glu Thr Ala Lys Glu Leu Ala Gln Arg
      50      55      60
Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu
65      70      75      80
Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val
      85      90      95
Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
      100      105      110
Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
      115      120      125
Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
      130      135      140
His Ile Gly Val Asp His Leu Gly His Phe Leu Leu Thr His Leu Leu
145      150      155      160
Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
      165      170      175
Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
      180      185      190
Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
      195      200      205
Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
      210      215      220
Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
225      230      235      240
Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
      245      250      255
Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
      260      265      270
Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
      275      280      285
Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg
290      295      300
Leu Trp Asp Val Ser Cys Asp Leu Leu Gly Leu Pro Ile Asp
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<210> 340

<211> 483

<212> DNA

<213> Homo sapien

<400> 340

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gtccaaacg tgacatcact gatgctcttc tcgggggtgc tgatggcccg cttgggtcacg      360
tgctcaatct cgccattcga ctcttgctcc aaactgtatg aagacacctg actgcacgtt      420

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<210> 341
<211> 344
<212> DNA
<213> Homo sapien

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attaatttaa taatttctga tgatggtttt atctgcagta atatgtatat catctattag 240
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<210> 342
<211> 592
<212> DNA
<213> Homo sapien

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cctggcaggt aaaccaatgc caagagagt atggaaacca ttggcaagac tttgttgatg 180
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<210> 343
<211> 382
<212> DNA
<213> Homo sapien

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aaaccaccaa gctgaaaaaa aa 382

<210> 344
<211> 536
<212> DNA
<213> Homo sapien

<400> 344
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<210> 345
 <211> 251
 <212> DNA
 <213> Homo sapien

<400> 345						
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<210> 346
 <211> 282
 <212> DNA
 <213> Homo sapien

<220>
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 <223> n = A,T,C or G

<400> 346						
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<210> 347
 <211> 201
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(201)
 <223> n = A,T,C or G

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<210> 348
 <211> 251
 <212> DNA
 <213> Homo sapien

<400> 348						
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<210> 349

<211> 251

<212> DNA

<213> Homo sapien

<400> 349

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cagaagggtc	tgaactctac	gtgttaccag	agaacataat	gcaattcatg	cattccactt	180
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<210> 350

<211> 908

<212> DNA

<213> Homo sapien

<400> 350

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<210> 351

<211> 472

<212> DNA

<213> Homo sapien

<400> 351

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<210> 352

<211> 251

<212> DNA

<213> Homo sapien

<400> 352

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<210> 353

<211> 436

<212> DNA

<213> Homo sapien

<400> 353

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<210> 354

<211> 854

<212> DNA

<213> Homo sapien

<400> 354

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gtgagtga	gatccccatt	ataggagcac	ttgggagaga	tcataataaa	gctgactctt	420
gagtacatgc	agtaatgggg	tagatgtgtg	tgggtgtgtc	tcattcctgc	aagggtgctt	480
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aaataacaaa	ggattgagaa	tcattgtgtc	taatgtataa	aagaccaggg	aaacataaat	720
atatcaactg	cataaatgta	aaatgcatgt	gaccacaaga	ggccccaag	tggcagacaa	780
cattgtaccc	attttccctt	ccaaaatgtg	agcggcgggc	ctgctgcttt	caaggctgtc	840
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<210> 355

<211> 676

<212> DNA

<213> Homo sapien

<400> 355

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atccacaagt	catacctgga	tgtcagcgaa	gagggcacgg	aggcagcagc	agccactggg	180
gacagcatcg	ctgtaaaaag	cctaccaatg	agagctcagt	tcaaggcgaa	ccaccccttc	240
ctgttcttta	taaggcacac	tcataccaac	acgatcctat	tctgtggcaa	gcttgccctc	300
ccctaatacag	atgggggttg	gtaagggtca	gagttgcaga	tgaggtgcag	agacaatcct	360
gtgactttcc	cacggccaaa	aagctgttca	cacctcacgc	acctctgtgc	ctcagtttgc	420

tcatctgcaa	aataggtcta	ggatttcttc	caaccatttc	atgagttgtg	aagctaaggc	480
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ggtgtctcat	ttgagtgtctg	tccagtgaca	tgatcaagtc	aatgagtaaa	attttaaggg	600
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<210> 356
 <211> 574
 <212> DNA
 <213> Homo sapien

<400> 356						
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caagcttccc	atttgtagat	ctcagtgccct	atgagtatct	gacacctgtt	cctctcttca	180
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aaaagtccac	aaaactgcag	tctttgctgg	gatagtaagc	caagcagtgc	ctggacagca	300
gagttctttt	cttgggcaac	agataaccag	acaggactct	aatcgtgctc	ttattcaaca	360
ttcttctgtc	tctgcctaga	ctggaataaa	aagccaatct	ctctcgtggc	acaggggaagg	420
agatacaagc	tctgtttacat	gtgatagatc	taacaaaggc	atctaccgaa	gtctgggtctg	480
gatagacggc	acagggagct	cttaggtcag	cgctgctggg	tggaggacat	tcctgagtc	540
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<210> 357
 <211> 393
 <212> DNA
 <213> Homo sapien

<400> 357						
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aagccacaac	caaracttga	ttttatcaac	aaaaaccctt	aaatataaac	ggsaaaaaag	180
atagatataa	ttattccagt	ttttttaaaa	cttaaaarat	attccattgc	cgaattaara	240
araarataag	tgttatatgg	aaagaagggc	attcaagcac	actaaaraaa	cctgaggkaa	300
gcataatctg	tacaaaatta	aactgtcctt	tttggcattt	taacaaattt	gcaacgktct	360
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<210> 358
 <211> 630
 <212> DNA
 <213> Homo sapien

<400> 358						
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gcatagagta	gggaagctaa	tccagcacag	ggaggtcaca	gagacatccc	taagggaagtg	180
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gaaagagagc	tagaacagct	ggagccgttc	tccggtgtaa	agaggagtca	aagagataag	360
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gggtagactg	gactaggtaa	gactggaggc	aggtagacct	cttctaaggc	ctgcgatagt	540
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<210> 359
 <211> 620
 <212> DNA

<213> Homo sapien

<400> 359

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aatgtaagat	aactttataa	gaattctggg	tcaaataaaa	ttctttgaag	aaaacatcca	480
aatgtcattg	acttatcaaa	tactatcttg	gcatataacc	tatgaaggca	aaactaaaca	540
aacaaaaagc	tcacacaaaa	caaaaccatc	aacttatitt	gtattctata	acatacgaga	600
ctgtaaagat	gtgacagtgt					620

<210> 360

<211> 431

<212> DNA

<213> Homo sapien

<400> 360

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tactcatcat	ttttggccag	cagttgtttg	atcaccaaac	atcatgccag	aatactcagc	180
aaaccttctt	agctcttgag	aagtcaaagt	ccgggggaat	ttattcctgg	caattttaat	240
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agtggacatg	cagtggcaga	gctcctggta	accacctaga	ggaatacaca	ggcacatgtg	360
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<210> 361

<211> 351

<212> DNA

<213> Homo sapien

<400> 361

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caatcctgga	ttcaatgtct	gaaacctcgc	tctctgcctg	ctggacttct	gaggccgtca	300
ctgccactct	gtcctccagc	tctgacagct	cctcatctgt	ggtcctgttg	t	351

<210> 362

<211> 463

<212> DNA

<213> Homo sapien

<400> 362

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ccccggtcac	agaaatgacc	aggttgggtg	ttttcagggt	ccagtgcctg	gtcagcagct	180
cgtaaaggat	ttccgcgtcc	gtgtcgcagg	acagacgtat	atacttccct	ttcttcccca	240
gtgtctcaaa	ctgaatatcc	ccaaaggcgt	cggtaggaaa	ttccttggtg	tgtttcttgt	300
agttccattt	ctcacttttg	ttgatctggg	tgcttccat	gtgctggctc	tgggcatagc	360
cacacttgca	cacattctcc	ctgataagca	cgatggtgtg	gacaggaagg	aaggatttca	420
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<210> 363
 <211> 653
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(653)
 <223> n = A,T,C or G

<400> 363
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 tgggaggcac tacgcaagat gggactgcgt cctgggggtga gacatcctct ccttgagat 180
 ctaacgaaac ttctcaccta tgagttgtaa agcagaaata cctgnactac agacgagtgc 240
 ccaacagcaa ccccccgga gtatgagttc ctctrgggcc tccgttccta ccatgagasc 300
 tagcaagatg naagtgttga gantcattgc agaggttcag aaaagagacc cntcgtgact 360
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 ctgaggccga agcccggtc gaagcaagaa cccgcatggg aattggagat gaggctgtgt 480
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 attttgaga tccntggtcc agaattccat ttacctctg ggccagatac caccagaatg 600
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<210> 364
 <211> 401
 <212> DNA
 <213> Homo sapien

<400> 364
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 aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga 180
 tgagaaagct caattataga tgcaaagtta taactaaact actatagtag taaagaaata 240
 catttcacac cttcatata aattcactat cttggcttga ggcactccat aaaatgtatc 300
 acgtgcatag taaatcttta tatttgctat ggcgttgac tagaggactt ggactgcaac 360
 aagtggatgc gcggaaaatg aaatcttctt caatagccca g 401

<210> 365
 <211> 356
 <212> DNA
 <213> Homo sapien

<400> 365
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 taccagagca tcaagtctct gcagcaggtc attcttgggt aaagaaatga cttccacaaa 180
 ctctccatcc cctggctttg gottcggcct tgcgttttcg gcatcatctc cgtaaatggt 240
 gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga 300
 acattcggca atgtcccctt tgtagccagt ttcttcttcg agctcccga gagcag 356

<210> 366
 <211> 1851
 <212> DNA
 <213> Homo sapien

<400> 366
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tcacttcctt	taagcctttg	tgactcttcc	tctgatgtca	gctttaagtc	ttgttctgga	180
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cagcaagtat	gagagcagtt	cttccatata	tatccagcgc	atttaaattc	gcttttttct	420
tgattaaaaa	tttcaccact	tgctgttttt	gctcatgtat	accaagtagc	agtggtgtga	480
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gctcctgaga	aacaccccag	ctcttccggt	ctaacacagg	caagtcaata	aatgtgataa	1620
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tttgacaaaa	tccagcatcc	ttgtatttat	tgttgacagtt	ctcagaggaa	atgcttctaa	1740
cttttcccca	tttagtatta	tggtggctgt	gggcttgtca	taggtggttt	ttattacttt	1800
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<210> 367

<211> 668

<212> DNA

<213> Homo sapien

<400> 367

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accrtataag	agcagtgcct	tggccattaa	tttatctttc	attrtagaca	gcrtagtgya	180
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catatcttag	gaattcaaaa	taacattcca	cagctttcac	caactagtta	tatttaaagg	360
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ctactgcata	cctttatcag	agctgtcctc	tttttgttgc	caaggacatt	aagttgacat	480
cgtctgtcca	gcaggagttt	tactacttct	gaattcccat	tggcagaggc	cagatgtaga	540
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<210> 368

<211> 1512

<212> DNA

<213> Homo sapien

<400> 368

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ttcaaacaga	ttggaaaccc	ggagttacct	gctagttggt	gaaactgggt	ggtagacgcg	180

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gaacatggca	ctgatccaaa	tattccagat	gagtatggaa	ataccactct	rcactaygct	960
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<210> 369

<211> 1853

<212> DNA

<213> Homo sapien

<400> 369

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gccttcatgg	akcccaggtg	ccacgtccrt	ggagaagatc	tggacaagct	ccacagagct	660
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aacaagargg	acaagcaaaa	gaggactgct	ctacatctgg	cctctgccaa	tgggaattca	780
gaagtagtaa	aactcstgct	ggacagacga	tgtcaactta	atgtccttga	caacaaaaag	840
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<210> 370

<211> 2184

<212> DNA

<213> Homo sapien

<400> 370

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<210> 371

<211> 1855

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)... (1855)

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<400> 371

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<210> 372

<211> 1059

<212> DNA

<213> Homo sapien

<400> 372

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<210> 373
 <211> 1155
 <212> DNA
 <213> Homo sapien

<400> 373

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<210> 374
 <211> 2000
 <212> DNA
 <213> Homo sapien

<400> 374

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<210> 375

<211> 2040

<212> DNA

<213> Homo sapien

<400> 375

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<210> 376

<211> 329

<212> PRT

<213> Homo sapien

<400> 376

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Gly	Lys	Val	Pro	Arg	Lys	Asp	Leu	Ile	Val	Met	Leu	Arg	Asp	Thr	Asp
	130					135					140				
Val	Asn	Lys	Arg	Asp	Lys	Gln	Lys	Arg	Thr	Ala	Leu	His	Leu	Ala	Ser
145					150					155					160
Ala	Asn	Gly	Asn	Ser	Glu	Val	Val	Lys	Leu	Val	Leu	Asp	Arg	Arg	Cys
			165					170					175		
Gln	Leu	Asn	Val	Leu	Asp	Asn	Lys	Lys	Arg	Thr	Ala	Leu	Thr	Lys	Ala
		180						185					190		
Val	Gln	Cys	Gln	Glu	Asp	Glu	Cys	Ala	Leu	Met	Leu	Leu	Glu	His	Gly
	195						200				205				
Thr	Asp	Pro	Asn	Ile	Pro	Asp	Glu	Tyr	Gly	Asn	Thr	Thr	Leu	His	Tyr
	210					215					220				
Ala	Val	Tyr	Asn	Glu	Asp	Lys	Leu	Met	Ala	Lys	Ala	Leu	Leu	Leu	Tyr
225					230					235					240
Gly	Ala	Asp	Ile	Glu	Ser	Lys	Asn	Lys	His	Gly	Leu	Thr	Pro	Leu	Leu
			245						250					255	
Leu	Gly	Ile	His	Glu	Gln	Lys	Gln	Gln	Val	Val	Lys	Phe	Leu	Ile	Lys
		260						265					270		
Lys	Lys	Ala	Asn	Leu	Asn	Ala	Leu	Asp	Arg	Tyr	Gly	Arg	Thr	Ala	Leu
	275					280					285				
Ile	Leu	Ala	Val	Cys	Cys	Gly	Ser	Ala	Ser	Ile	Val	Ser	Pro	Leu	Leu
	290					295					300				
Glu	Gln	Asn	Val	Asp	Val	Ser	Ser	Gln	Asp	Leu	Glu	Arg	Arg	Pro	Glu
305					310					315					320
Ser	Met	Leu	Phe	Leu	Val	Ile	Ile	Met							
				325											

<210> 377

<211> 148

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(148)

<223> Xaa = Any Amino Acid

<400> 377

Met	Thr	Xaa	Pro	Ser	Trp	Ser	Pro	Gly	Thr	Thr	Ser	Val	Glu	Lys	Ile
1			5					10					15		
Trp	Thr	Ser	Ser	Thr	Glu	Leu	Pro	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys
		20					25					30			
Asp	Leu	Ile	Val	Met	Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Xaa	Asp	Lys

125

35 40 45
 Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu
 50 55 60
 Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp
 65 70 75 80
 Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp
 85 90 95
 Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro
 100 105 110
 Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp
 115 120 125
 Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser
 130 135 140
 Lys Asn Lys Val
 145

<210> 378
 <211> 1719
 <212> PRT
 <213> Homo sapien

<400> 378
 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
 1 5 10 15
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
 20 25 30
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
 35 40 45
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
 50 55 60
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
 65 70 75 80
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
 85 90 95
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
 100 105 110
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
 115 120 125
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
 130 135 140
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
 145 150 155 160
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
 165 170 175
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
 180 185 190
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
 195 200 205
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
 210 215 220
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
 225 230 235 240
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
 245 250 255
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
 260 265 270
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
 275 280 285

Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
 290 295 300
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
 305 310 315 320
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
 325 330 335
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
 340 345 350
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile
 355 360 365
 Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys
 370 375 380
 Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser
 385 390 395 400
 Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys
 405 410 415
 Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly
 420 425 430
 Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys
 435 440 445
 Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly
 450 455 460
 Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys
 465 470 475 480
 Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys
 485 490 495
 Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp
 500 505 510
 Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu
 515 520 525
 Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp
 530 535 540
 Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln
 545 550 555 560
 Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val
 565 570 575
 Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn
 580 585 590
 Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu
 595 600 605
 Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp
 610 615 620
 Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys
 625 630 635 640
 Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys
 645 650 655
 Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys
 660 665 670
 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala
 675 680 685
 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly
 690 695 700
 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser
 705 710 715 720
 Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser
 725 730 735
 His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln
 740 745 750

Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys
 755 760 765
 Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser
 770 775 780
 Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp
 785 790 795 800
 Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly
 805 810 815
 Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn
 820 825 830
 Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe
 835 840 845
 Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser
 850 855 860
 Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn
 865 870 875 880
 Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu
 885 890 895
 Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile
 900 905 910
 Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn
 915 920 925
 Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro
 930 935 940
 Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu
 945 950 955 960
 Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe
 965 970 975
 Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His
 980 985 990
 Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser
 995 1000 1005
 Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu
 1010 1015 1020
 Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His
 1025 1030 1035 1040
 Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met
 1045 1050 1055
 Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met
 1060 1065 1070
 Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys
 1075 1080 1085
 Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr
 1090 1095 1100
 Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys
 1105 1110 1115 1120
 Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp
 1125 1130 1135
 Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His
 1140 1145 1150
 Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp
 1155 1160 1165
 Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg
 1170 1175 1180
 Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val
 1185 1190 1195 1200
 Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys
 1205 1210 1215

Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly
 1220 1225 1230
 Asn Ser Glu Val Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn
 1235 1240 1245
 Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys
 1250 1255 1260
 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro
 1265 1270 1275 1280
 Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr
 1285 1290 1295
 Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp
 1300 1305 1310
 Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val
 1315 1320 1325
 His Glu Gln Lys Gln Gln Val Lys Phe Leu Ile Lys Lys Lys Ala
 1330 1335 1340
 Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala
 1345 1350 1355 1360
 Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn
 1365 1370 1375
 Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr
 1380 1385 1390
 Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr
 1395 1400 1405
 Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu
 1410 1415 1420
 Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly
 1425 1430 1435 1440
 Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn
 1445 1450 1455
 Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser
 1460 1465 1470
 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly
 1475 1480 1485
 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu
 1490 1495 1500
 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys
 1505 1510 1515 1520
 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser
 1525 1530 1535
 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu
 1540 1545 1550
 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser
 1555 1560 1565
 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe
 1570 1575 1580
 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe
 1585 1590 1595 1600
 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly
 1605 1610 1615
 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro
 1620 1625 1630
 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln
 1635 1640 1645
 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile
 1650 1655 1660
 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser
 1665 1670 1675 1680

Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn
 1685 1690 1695
 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr
 1700 1705 1710
 Met Lys His Gln Ser Gln Leu
 1715

<210> 379
 <211> 656
 <212> PRT
 <213> Homo sapien

<400> 379
 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
 1 5 10 15
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
 20 25 30
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
 35 40 45
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
 50 55 60
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
 65 70 75 80
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
 85 90 95
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
 100 105 110
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
 115 120 125
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
 130 135 140
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
 145 150 155 160
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
 165 170 175
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
 180 185 190
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
 195 200 205
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
 210 215 220
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
 225 230 235 240
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
 245 250 255
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
 260 265 270
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
 275 280 285
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
 290 295 300
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala S r Ile
 305 310 315 320
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
 325 330 335
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val
 340 345 350
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile

355 360 365
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu
 370 375 380
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys
 385 390 395 400
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu
 405 410 415
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn
 420 425 430
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro
 435 440 445
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu
 450 455 460
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu
 465 470 475 480
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
 485 490 495
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
 500 505 510
 Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys
 515 520 525
 Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly
 530 535 540
 Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser
 545 550 555 560
 Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr
 565 570 575
 His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln
 580 585 590
 Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln
 595 600 605
 Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys
 610 615 620
 Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile
 625 630 635 640
 Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
 645 650 655

<210> 380

<211> 671

<212> PRT

<213> Homo sapien

<400> 380

Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys
 1 5 10 15
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe
 20 25 30
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
 35 40 45
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
 50 55 60
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
 65 70 75 80
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
 85 90 95
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
 100 105 110

Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe
 115 120 125
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His
 130 135 140
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met
 145 150 155 160
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala
 165 170 175
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu
 180 185 190
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr
 195 200 205
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met
 210 215 220
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn
 225 230 235 240
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys
 245 250 255
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly
 260 265 270
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val
 275 280 285
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr
 290 295 300
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile
 305 310 315 320
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu
 325 330 335
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Val
 340 345 350
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile
 355 360 365
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu
 370 375 380
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys
 385 390 395 400
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu
 405 410 415
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn
 420 425 430
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro
 435 440 445
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu
 450 455 460
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu
 465 470 475 480
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp
 485 490 495
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu
 500 505 510
 Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp
 515 520 525
 Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys
 530 535 540
 His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala
 545 550 555 560
 Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg
 565 570 575

Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His
 580 585 590
 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn
 595 600 605
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile
 610 615 620
 Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys
 625 630 635 640
 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala
 645 650 655
 Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
 660 665 670

<210> 381

<211> 251

<212> DNA

<213> Homo sapien

<400> 381

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ggtaacatgc	ttcccctaag	ggtatcccaa	cccagggggc	tcacatgac	ctctgagggg	120
ccaatatccc	aggagaagca	ttggggagtt	gggggcaggt	gaaggaccca	ggactcacac	180
atcctggggc	tccaaggcag	aggagagggt	cctcaagaag	gtcaggagga	aaatccgtaa	240
caagcagtca	g					251

<210> 382

<211> 3279

<212> DNA

<213> Homo sapiens

<400> 382

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cactgggagg	ggacatcctg	cagaaggtag	gagttagcaa	acaccgctg	caggggagg	180
gagagccctg	cggcacctgg	gggagcagag	ggagcagcac	ctggccaggc	ctgggaggag	240
gggcctggag	ggcgtgagga	ggagcgagg	ggctgcatgg	ctggagtgag	ggatcagggg	300
cagggcgaga	gatggcctca	cacagggaag	agagggcccc	tctgcaggg	cctcacctgg	360
gccacaggag	gacactgctt	ttcctctgag	gagtcaggag	ctgtggatgg	tgctggacag	420
aagaaggaca	gggcctggct	caggtgtcca	gaggctgtcg	ctggcttccc	tttgggatca	480
gactgcaggg	agggagggcg	gcagggttgt	ggggggagtg	acgatgagga	tgacctgggg	540
gtggctccag	gccttgcccc	tgccctgggc	ctcaccagc	ctccctcaca	gtctcctggc	600
cctcagtcct	tccctccac	tccatcctcc	atctggcctc	agtgggtcat	tctgatcact	660
gaactgacca	taccagccc	tgcccacggc	cctccatggc	tccccaatgc	cctggagagg	720
ggacatctag	tcagagagta	gtcctgaaga	ggtggcctct	gcgatgtgcc	tgtgggggca	780
gcacctgca	gatggctccg	gccctcatcc	tgctgacctg	tctgcaggga	ctgtcctcct	840
ggaccttgcc	ccttgtgcag	gagctggacc	ctgaagtccc	ctccccatag	gccaagactg	900
gagccttggt	ccctctgttg	gactccctgc	ccatattctt	gtgggagtg	gttctggaga	960
catttctgtc	tgctcctgag	agctgggaat	tgctctcagt	catctgcctg	cgcggttctg	1020
agagatggag	ttgcctaggc	agttattggg	gccaatcttt	ctcactgtgt	ctctcctcct	1080
ttacccttag	ggtgattctg	ggggccact	tgcttgtaat	ggtgtgcttc	aaggtatcac	1140
atcatggggc	ctcgaccat	gtgccctgcc	tgaaaagcct	gctgtgtaca	ccaagtggt	1200
gcattaccgg	aagtggatca	aggacaccat	cgcagccaac	ccctgagtg	ccctgtccca	1260
cccctacctc	tagtaaattt	aagtccacct	cacgttctgg	catcacttgg	cctttctgga	1320
tgctggacac	ctgaagcttg	gaactcacct	ggccgaagct	cgagcctcct	gagtcctact	1380
gacctgtgct	ttctggtgtg	gagtcagggg	ctgctaggaa	aaggaatggg	cagacacagg	1440
tgtatgccaa	tgtttctgaa	atgggtataa	tttcgtcctc	tccttcggaa	cactggctgt	1500
ctctgaagac	ttctcgtctc	gtttcagtga	ggacacacac	aaagacgtgg	gtgaccatgt	1560
tgtttgtggg	gtgcagagat	gggagggggt	gggccacccc	tggaagagtg	gacagtgaca	1620

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caagggtggac actctctaca gatcactgag gataagctgg agccacaatg catgaggcac 1680
acacacagca aggttgacgc tgtaaacata gccacgctg tcctgggggc actgggaagc 1740
ctagataagg ccgtgagcag aaagaagggg aggtcctcc tatgttggtg aaggaggggac 1800
tagggggaga aactgaaagc tgattaatta caggaggttt gttcaggtcc cccaaaccac 1860
cgtcagattt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgtggt 1920
ttattatggt ttgttacatt gataggatac atactgaaat cagcaaaca aacagatgta 1980
tagattagag tgtggagaaa acagaggaaa acttgcaagt acgaagactg gcaacttggc 2040
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gtgtccaggg tttttactgg gggctctgag gacgagtatg gagtacttga ataattgacc 2340
tgaagtcctc agacctgagg ttccctagag ttcaaacaga tacagcatgg tccagagtcc 2400
cagatgtaca aaaacaggga ttcatcaca atcccatctt tagcatgaag ggtctggcat 2460
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atcattgttt tatttgcctt cttttcacac cattgtgag ggagggatta ccacctggg 2820
gttatgaaga tggttgaaca ccccacacat agcaccggag atatgagatc aacagtttct 2880
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cccagctgat agaggaagta gccagggtggg agcctttccc agtgggtgtg ggacatatct 3180
ggcaagattt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
gttttcagac cttaaaaaaa aaaaaaaaaa aaaagtttt 3279

```

<210> 383

<211> 154

<212> PRT

<213> Homo sapiens

<400> 383

```

Met Ala Gly Val Arg Asp Gln Gly Gln Gly Ala Arg Trp Pro His Thr
          5                      10                      15

```

```

Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
          20                      25                      30

```

```

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
          35                      40                      45

```

```

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
          50                      55                      60

```

```

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
          65                      70                      75                      80

```

```

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
          85                      90                      95

```

```

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
          100                     105                     110

```

```

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
          115                     120                     125

```

Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu
 145 150

<210> 384
 <211> 557
 <212> DNA
 <213> Homo sapiens

<400> 384
 ggatcctcta gagcggccgc ctactactac taaattcgcg gccgcgtcga cgaagaagag 60
 aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120
 ggggaagggt cccttttgca ttgccaagt ccataaccat gagcactact ctaccatggg 180
 tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240
 acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
 ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttgc 360
 tccccaaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc 420
 ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaagt 480
 tcaattgtga aatgaatat catgcaaata aattatgcga ttttttttcc aaagtaaaaa 540
 aaaaaaaaa aaaaaaa 557

<210> 385
 <211> 337
 <212> DNA
 <213> Homo sapiens

<400> 385
 ttcccaggtg atgtgcgagg gaagacacat ttactatcct tgatggggct gattccttta 60
 gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120
 tctcaaagcc atctgctgtc ttcgagtacg gacacatcat cactcctgca ttgttgatca 180
 aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
 tatcagacag gtccagtttc cgcaccaaca cctgctgggt ccctgtcgtg gtctggatct 300
 ctttggccac caattcccc tttccacat cccggca 337

<210> 386
 <211> 300
 <212> DNA
 <213> Homo sapiens

<400> 386
 gggcccgtcta ccggcccagg ccccgccctcg cgagtcctcc tccccgggtg cctgcccgca 60
 gcccgctcgg ccagaggggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120
 gcgaccttgg ccgaaggct cttagcaagga cccaccgacc ccagccgcgg cggcgcgggc 180
 gcggactttg ccggtgtgt gggcgggagc ggactgctg tccgcggacg ggcagcgaag 240
 atgttagcct tcgctgccag gaccgtggac cgatcccagg gctgtggtgt aacctcagcc 300

<210> 387
 <211> 537
 <212> DNA
 <213> Homo sapiens

<400> 387
 gggccgagtc gggcaccaag ggactctttg caggcttctt tctcggatc atcaaggctg 60
 cccctctctg tgccatcatg atcagcacct atgagttcgg caaaagcttc ttccagaggc 120

```

tgaaccagga cgggcttctg ggcggctgaa aggggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ccttttctc agcactgagg 240
gagggggctt gtttcccttc cctcccgcg acaagctcca gggcagggct gtccctctgg 300
gcggcccagc acttcctcag acacaacttc ttctgctgc tccagtcgtg gggatcatca 360
cttaccacc cccaagttc aagaccaa atctccagctg ccccttctgt gtttccctgt 420
gtttgctgta gctgggcatg totccaggaa ccaagaagcc ctcagcctgg ttagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaa aaaaaa 537

```

<210> 388

<211> 520

<212> DNA

<213> Homo sapiens

<400> 388

```

aggataattt ttaaaccaat caaatgaaaa aaacaaacaa acaaaaaagg aaatgtcatg 60
tgagggttaa ccagtttgca ttccccta atgtggaaaa taagaggact actcagcact 120
gtttgaagat tgccctctt acagcttctg agaattgtgt tatttcactt gccaaagtga 180
ggaccccctc cccaacatgc ccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctacca gagaccagga gggtttggtt agctcacagg 300
acttccccca cccagaaga ttagcatccc atactagact cataactcaac tcaactaggc 360
tcataactca ttgatgggta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttta tgggtgggtt ttttctggt 520

```

<210> 389

<211> 365

<212> DNA

<213> Homo sapiens

<400> 389

```

cgttgcccc gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaaggc tggatttcag atctgcctgg ttccagccgc agtggtgccct ctgctcccc 120
aacgactttc caaataatct caccagcgcc ttccagctca ggcgtcctag aagcgtcttg 180
aagcctatgg ccagctgtct ttgtgttccc tctccccgc ctgtcctcac agctgagact 240
cccaggaaac cttcagacta ctttctctg cttcagcaa ggggcgttgc ccacattctc 300
tgagggctcag tggagaagacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag

```

<210> 390

<211> 221

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(221)

<223> n = A, T, C or G

<400> 390

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tgccctctcca tcttgcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggnnt ctcattgggtg tggaaacatct ctgcttgccg ttccaggaag gcctctggct 120
gctctangag tctgancnga ntctgtgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

```

<210> 391

<211> 325

<212> DNA

<213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(325)
 <223> n = A,T,C or G

<400> 391
 tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgnega tgcangcttt 60
 ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
 tagccagggc actgctgcc aacagccagtc cnaataccat catgtnaccc ggtgngctct 180
 naantngat ntccanagcc ctacccatcn tagttctgct ctcccaccgg ntaccagccc 240
 cactgcccag gaatcctaca gccagtaccc tgtcccagcg tctctaccta ccagtacgat 300
 gagacctccg gctactacta tgacc 325

<210> 392
 <211> 277
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(277)
 <223> n = A,T,C or G

<400> 392
 atattgttta actccttccct ttatatcttt taacattttc atggngaaaag gttcacatct 60
 agtctcactt nggcnagnn ctcctacttg agtctcttcc cgggcctggn ccagtnagnaa 120
 antaccanga accgncatgn cttanaaach ncctgggttn tgggttnntc aatgactgca 180
 tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240
 ctgaggatac agcgccgcgt cctgtgttgc tggggaa 277

<210> 393
 <211> 566
 <212> DNA
 <213> Homo sapiens

<400> 393
 actagtccag tgtggtggaa ttccgcccgc cgctcgacga caggtcagct gtctggctca 60
 gtgatctaca ttctgaagtt gtctgaaaat gtcttcata ttaaattcag cctaaacggt 120
 ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
 gagaaggtct agtttgtcca tcagcattat catgatata ggactgggta ctgtgttaag 240
 gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300
 ggggtggttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
 catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
 ttctgcctca atgtttactg tgcctttgtt tttgctagtt tgtgttgttg aaaaaaaaaa 480
 cattctctgc ctgagtttta atttttgtcc aaagttattt taatctatac aattaaaagc 540
 ttttgcctat caaaaaaaaa aaaaaa 566

<210> 394
 <211> 384
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(384)
 <223> n = A,T,C or G

<400> 394

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gaacatacat gtcccggcac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaattng gaccggggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttta ggagttttta gctgagtgtc actgtagacc ccaaatacca 180
tccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaa ttaccattac 300
agggtagcaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt 384

```

<210> 395

<211> 399

<212> DNA

<213> Homo sapiens

<400> 395

```

ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgc 60
tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttctct ttggaaagcc tgggcatctc ctactacag acctctgacc atgggacggg 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac 399

```

<210> 396

<211> 403

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(403)

<223> n = A,T,C or G

<400> 396

```

tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtggag gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt 403

```

<210> 397

<211> 100

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(100)

<223> n = A,T,C or G

<400> 397

```

actagtnacg tgtgggtggaa ttgcgggccg cgtgcaccta naanccatct ctatagcaaa 60
tccatccccg ctcttggttg gtnacagaat gactgacaaa 100

```

<210> 398

<211> 278

<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(278)
<223> n = A,T,C or G

<400> 398
gcggccgcgt cgacagcagt tccgccagcg ctcccccctg ggtgggggatg tgctgcacgc 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
tcaactactgt gcctcgacca gtgaggagag ctggaccgac agcgagggtgg actcatcatg 180
ctccggggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg 278

<210> 399
<211> 298
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(298)
<223> n = A,T,C or G

<400> 399
acggagggtgg aggaagcgnc cctgggatcg anaggatggg tectgncatt gaccncctcn 60
gggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcgtgggct 180
ccggcattga gcgcatgggc ccgctgggccc tgcaccacat ggcctccanc attgancgca 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcattggg 298

<210> 400
<211> 548
<212> DNA
<213> Homo sapiens

<400> 400
acatcaacta cttcctcatt ttaaggatat gcagttccct tcateccctt ttcctgcctt 60
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaagg 120
caaagaacca cagcttaga agggtaagag ggcaccctat gaaatgaaat ggtgatttct 180
tgagtctctt tttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240
tgcagagggc tagagaatta tttcatacag gctttgaggc caccatgtc acttatcccg 300
tataccctct caccatcccc ttgtctactc tgatgcccc aagatgcaac tgggcagcta 360
gttggcccca taattctggg cttttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccagtg atctctacc atgggcccc ctcctgggat caagccctc ccaggccctg 480
tccccagccc ctctgcccc agcccccccg cttgccttgg tgctcagccc tccattggg 540
agcaggtt 548

<210> 401
<211> 355
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A,T,C or G

<400> 401
actgtttcca tggtatgttt ctacacattg ctacctcagt gctcctggaa acttagcttt 60
tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
taagagtggg ggctattttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtggcc atgggtggcg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300
cccttttgcg ttgccaagtg ccataacctat gagcactact ctaccatggn tctgc 355

<210> 402
<211> 407
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(407)
<223> n = A,T,C or G

<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tggtgtcttc aagaaaccca 60
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa 407

<210> 403
<211> 303
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 403
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcaccaa 60
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcataaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tcttaacaac gaccgaaacc cattatttac ataaacctcc attcggtaac catgttgaaa 300
gga 303

<210> 404
<211> 225
<212> DNA
<213> Homo sapiens

<400> 404
aagtgtact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60
attgttaatg cactcattta cctttacatg gtgaaagtgc tctcttgatc ctacaaacag 120
acattttcca ctggtgtttc catagtgtgt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat 225

<210> 405

<211> 334
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(334)
 <223> n = A,T,C or G

<400> 405
 gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgaggggtg tctggaggac 60
 ttcaatacac ctccccccat agtgaatcag cttccagggg gtccagtcct tctccttact 120
 tcatcccatat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
 ttcccagtgct ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
 ctggtgagggt tgtgcctcga gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
 cactctccac tctctcanng tggatccac, ccct 334

<210> 406
 <211> 216
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(216)
 <223> n = A,T,C or G

<400> 406
 ttctatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
 gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
 acnaaacaca aattttnatgt tgcacccttg ttctacacc tgtgggttat gacaaagaca 180
 actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407
 <211> 413
 <212> DNA
 <213> Homo sapiens

<400> 407
 gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
 gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
 gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
 cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
 ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
 tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
 tgggagttcc agaaaaagtt aaaacagaca atgggcccagg ttctgtagta aag 413

<210> 408
 <211> 183
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(183)
 <223> n = A,T,C or G

<400> 408

```

ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tnccttaacta gttaatcctt aaagggtctan ntaatcctta actagtcctt ccattgtgag 120
cattatcctt ccagtattcn ccttctnttt tatttactcc ttcttggtta cccatgtact 180
ntt 183

```

<210> 409

<211> 250

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 409

```

cccacgcatg ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
ggccttatgc 250

```

<210> 410

<211> 306

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(306)

<223> n = A,T,C or G

<400> 410

```

ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtcttgcaa tccatttgc aggatccgtc tgtgcacatg cctctgtaga gaggcagatt 120
cccagggacc ttggaaacag ttggcactgt aaagtgcttg ctcccaga caccatcctaa 180
aagggtgtgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atctttttta aactggaaag ttcaattgng aaaatgaata 300
tentgc 306

```

<210> 411

<211> 261

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(261)

<223> n = A,T,C or G

<400> 411

```

agagatattn cttaggtnaa agttcataga gtteccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaagtgc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggngaggcaa a 261

```

<210> 412

<211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 412
 gttcaatggt acctgacatt tctacaacac ccactcacc gatgtattcg ttgccagtg 60
 ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgccagg aaatactacg 120
 actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
 ctgggagatt tcaactggga cattgaattc ccaaactacc cangcaatta cccagccaac 240
 a 241

<210> 413
 <211> 231
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(231)
 <223> n = A,T,C or G

<400> 413
 aactcttaca atccaagtga ctcatctgtg tgcttgaatc cttccactg tctcatctcc 60
 ctcatccaag tttctagtag cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
 aagtttactc tcctcatttg gaacctaaaa actctcttct tcctgggtct gaggggtcca 180
 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414
 <211> 234
 <212> DNA
 <213> Homo sapiens

<400> 414
 actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
 gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120
 gtgagccaag gagggagggt cttccttttg catgggatgg ggatgaagta aggagaggga 180
 ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca 234

<210> 415
 <211> 217
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(217)
 <223> n = A,T,C or G

<400> 415
 gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
 caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cacttttctca 120
 cacctagcaa tagtagaatt cagtctact tctgaggcca gaagaatggt tcagaaaaat 180
 antggattat aaaaaataac aattaagaaa aataatc 217

<210> 416
 <211> 213
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(213)
 <223> n = A,T,C or G

<400> 416
 atgcataatnt aaagganact gcctcgcttt tagaagacat ctgggctgct ctctgcatga 60
 ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120
 cgaatgcag gtgggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
 atattggaac agatggagtc tctactacaa aag 213

<210> 417
 <211> 303
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(303)
 <223> n = A,T,C or G

<400> 417
 nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60
 gtgggaaagg ctttactctg agttcaaata ttcaagccca tcagagagtc cacactggag 120
 agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180
 ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
 tcantcaaag ttctgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
 agt 303

<210> 418
 <211> 328
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(328)
 <223> n = A,T,C or G

<400> 418
 tttttggcgg tgggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
 tgcacaggca tgatctcggc tcaactacaac ccctgcctcc catgtccaag cgattcttgt 120
 gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacacca gctagttttt 180
 gtatttttag tagagacagg gtttcacat gttggccagg ctggtctcaa actcctnacc 240
 tcagnngtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300
 aaagtgctan gattacaggc cgtgagcc 328

<210> 419
 <211> 389
 <212> DNA
 <213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(389)

<223> n = A,T,C or G

<400> 419

```
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatt 60
accctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct gatcttgctg 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggg gtgccaggca 240
ccggttctcc agccaccaac ctcaactcgt cccgcaaatg gcacatcagt tcttctaccc 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg 389
```

<210> 420

<211> 408

<212> DNA

<213> Homo sapiens

<400> 420

```
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtgtt tgacttttgt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccoc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gattcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgtctat acaaacctgg caagcccg 408
```

<210> 421

<211> 352

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(352)

<223> n = A,T,C or G

<400> 421

```
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggctt tttttgggtc cttcttctcc accacnata acttgcatgc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacagggt tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcagtc tcacaagttg gcangtctgc 300
cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttctt gg 352
```

<210> 422

<211> 337

<212> DNA

<213> Homo sapiens

<400> 422

```
atgccaccat gctggcaatg cagcgggagg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaaggc gtgggtcaagg 120
gcgatagcaa ggtgcggggc atcgcggggc cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggtc 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacggcg attcacggac 300
gcttcttcgg ccggtacggc tggcctatga aaattat 337
```

<210> 423
 <211> 310
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(310)
 <223> n = A,T,C or G

<400> 423
 gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
 aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
 tcaactgaag aacagggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtcc 180
 tccttcttga agattctttg gcagttgtct ttgtcataac ccacagggtgt anaaacaagg 240
 gtgcaacatg aaatttctgt ttctagtagca gtgcatgtct cacagttgtc aagtctgccc 300
 tccgagttta 310

<210> 424
 <211> 370
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(370)
 <223> n = A,T,C or G

<400> 424
 gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
 ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120
 cactgacaga acagggtctt ttttgggtcc ttcttctccac cacgatatac ttgcagtcc 180
 ccttcttgaa gattcttttg cagttgtctt tgtcataacc cacagggtga gaaacatcct 240
 ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
 cacgaagggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
 tccgtcgacg 370

<210> 425
 <211> 216
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(216)
 <223> n = A,T,C or G

<400> 425
 aattgctatn ntttattttg ccaactcaaaa taattaccaa aaaaaaaaaa tnttaaatga 60
 taacaacnca acatcaaggn aananaaca ggaatggntg actntgcata aatnggccga 120
 anattatcca ttatnttaag ggttgacttc aggntacagc acacagacaa acatgcccag 180
 gagntntca ggaccgctcg atgtntntg aggagg 216

<210> 426
 <211> 596
 <212> DNA
 <213> Homo sapiens

```

<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gcccgaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggcc ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaaccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgtgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct 596

```

<210> 427

<211> 107

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(107)

<223> n = A,T,C or G

<400> 427

```

gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagn 107

```

<210> 428

<211> 38

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(38)

<223> n = A,T,C or G

<400> 428

```

gaacttcna anaangactt tattcactat ttacatt 38

```

<210> 429

<211> 544

<212> DNA

<213> Homo sapiens

<400> 429

```

ctttgctgga cggaataaaa gtggacgcaa gcatgaccto ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctactcacc atcctctcct gttggttctg tgctgcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatattt ttgccagggtg gtaggagaga 540
ttat 544

```

<210> 430

<211> 507
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(507)
 <223> n = A,T,C or G

<400> 430
 cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
 gaacactgac acccatcttc caccgccgaca ctctgattta attgggctgc agtgagaaca 120
 gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
 ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
 attcaactag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
 caagaaggag gactgcaagt atatcgtggg ggagaagaag gacccaaaaa agacctgttc 360
 tgtcagtga tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
 cattctctc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480
 ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431
 <211> 392
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(392)
 <223> n = A,T,C or G

<400> 431
 gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
 aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
 tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
 aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
 catcattcca gcattctgag attaggngga ttggggatca ttctggagtt ggaatgttca 300
 acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaagg 360
 gcaatgagtc tggctttttac tctgtgtgtt ct 392

<210> 432
 <211> 387
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(387)
 <223> n = A,T,C or G

<400> 432
 ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
 aaatgcaagg caacatgtgt agatctcttt tcttattctt ttgtctataa tactgtattg 120
 ngtagtccaa gctctcgna gtccagccac tngaaacat gtcctctta gattaacctc 180
 gtggacnctn ttgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240
 attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
 atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
 acaacgtata gaacactgga gtccttt 387

<210> 433
 <211> 281
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(281)
 <223> n = A,T,C or G

<400> 433
 ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
 ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
 caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180
 atcgccgtgg ctattcctcn ttgntattac accagngagg ntctctgtnt gcccaactgg 240
 tnnaaaaccg ntatacaata atgatagaat aggacacaca t 281

<210> 434
 <211> 484
 <212> DNA
 <213> Homo sapiens

<400> 434
 ttttaaaata agcatttagt gctcagtcct tactgagtag tctttctctc ccctcctctg 60
 aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
 tggtgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
 tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
 agctagtcta tcagcatctg acagggtgaat tggatggttc tcagaaccat ttcaccaga 300
 cagcctgttt ctatcctgtt taataaatta gtttggttct tctacatgca taacaaaccc 360
 tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
 tttatttttc tatgtgtttt ttgcacataa tgagtgtttt gaaaataaag taccatgtc 480
 tttta 484

<210> 435
 <211> 424
 <212> DNA
 <213> Homo sapiens

<400> 435
 gcgccgtca gagcaggtca ctttctgcct tccacgtcct ccttcaagga agccccatgt 60
 gggtagcttt caatatcgca gggtcttact cctctgcctc tataagctca aaccaccaa 120
 cgatcgggca agtaaaccgc ctccctcgcc gacttcggaa ctggcgagag ttcagcgag 180
 atgggcctgt ggggaggggg caagatagat gagggggagc ggcaggtgtc ggggtgacc 240
 cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggcct 300
 ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
 gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420
 aaac 424

<210> 436
 <211> 667
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_f ature
 <222> (1)...(667)
 <223> n = A,T,C or G

<400> 436

```
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcctcttct ggaattcctc tgatttcaaa gtctcactct caagttcttg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacaggggt 300
gccaggtttg tcatagcact catcaaagtc cggtcacagt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaagggt tcaatgggac ttcgggtccc atgccgaac 540
accaaagtca caaacttcaa ctccctgggt agtacacttc ggtctagcca gaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag 667
```

<210> 437

<211> 693

<212> DNA

<213> Homo sapiens

<400> 437

```
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaaact tcagacagct ttttcagatc 180
ataaaagata attcttagcc catgttcttc tccagagcag acctgaaatg acagcacagc 240
aggtactcct ctattttcac cctcttggt tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttgggggggac agccagcatc tttagctttc 420
atttgatttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc 693
```

<210> 438

<211> 360

<212> DNA

<213> Homo sapiens

<400> 438

```
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcc aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
```

<210> 439

<211> 431

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(431)

<223> n = A,T,C or G

<400> 439

```
gttcctnnta actcctgcc aagacagctc tcctcaacat gagagctgca cccctcctcc 60
```

150

```

tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcattggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t                                     431

```

<210> 440

<211> 523

<212> DNA

<213> Homo sapiens

<400> 440

```

agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaaggga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaaattaa aacctctttg tgtcccttgg tcttggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaac acatatagca gctcttgaag 480
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<210> 441

<211> 430

<212> DNA

<213> Homo sapiens

<400> 441

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tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcattggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
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<210> 442

<211> 362

<212> DNA

<213> Homo sapiens

<400> 442

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ctaaggaatt agtagtggtc ccatcacttg tttggagtgt gctatttctaa aagattttga 60
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cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgttttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
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tc                                     362

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<210> 443

<211> 624

<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(624)
<223> n = A,T,C or G

<400> 443
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ttgaaagaat taaattcaga ggaggggaga gaaagagtag tcagtaggga ctgagcacta 120
aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcagggtacc ctgccttttg 180
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atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaata 480
agtacagaga gagggcactt aaaccaacta agggcctgga ggggaagggtt cctggaaaga 540
ngatgcttgt gctgggtcca aatcttgggc tactatgacc ttggccaaat tatttaaact 600
ttgtccctat ctgctaaaca gatc 624

<210> 444
<211> 425
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(425)
<223> n = A,T,C or G

<400> 444
gcacatcatt nntcttgcatt tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtgggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagagggttg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
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cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcacacctg gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga 425

<210> 445
<211> 414
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(414)
<223> n = A,T,C or G

<400> 445
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tgaaattctt tgcatgtggc agattattgg atgtagtttc ctttaactag catataaatc 180
tggtgtgttt cagataaatg aacagcaaaa tgtgggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatcctactc acaaatgact aggcttctcc tcttgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag 414

<210> 446

<211> 631
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(631)
<223> n = A,T,C or G

<400> 446
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60
tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcagggtgtg 120
atgctgggta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttggtc 180
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ctgtcactgt tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300
actgagattt gtaaactttc caaccttcca ggaaatgcc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgagggt 420
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttggc ctacacaata 480
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgacctg catttggtgt 540
aatctacacc aatgaaaaca tgtactacag ctatatattga ttatgtatgg atatatttga 600
aatagtatac attgtcttga tgttttttct g 631

<210> 447
<211> 585
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(585)
<223> n = A,T,C or G

<400> 447
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gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
agttcctgaa aggcagggtat agcaactgat cttcagaaag aggaactgtg tgcaccggga 240
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gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480
attcctttat ggggtcagtg ggaaagggtg caatgggact tcggtctcca tgccgaaaca 540
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta 585

<210> 448
<211> 93
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(93)
<223> n = A,T,C or G

<400> 448
tgctcgtggg tcattctgan ncccgaactg accntgcccag ccctgccgan gggccnccat 60
ggctccctag tgccctggag agganggggc tag 93

<210> 449
 <211> 706
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(706)
 <223> n = A,T,C or G

<400> 449
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 ttctganac cgaactgacc atgccagccc tgccgatggt cctccatggc tccctagtgc 120
 cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180
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 gtgctgcaag gcgattaagt tgggtaacgc caggggtttc ccagtncga cgttgtaaaa 360
 cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcattgcacg 420
 cgtacgtaag cttggatcct cttagagcggc cgcctactac tactaaattc gcggccgcgt 480
 cgacgtggga tccnactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540
 cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600
 aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660
 gcatggatga cagagtgaat ctccatctta aaaaaaaaaa aaaaaa 706

<210> 450
 <211> 493
 <212> DNA
 <213> Homo sapiens

<400> 450
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 aaatgaggct gagaacttta caaaggagtc ttacagacat gtccgccaata tcaactgcatg 180
 agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
 caagtcagggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300
 agagacactg tcagagagtt aaaaagttag ttctatccat gaggtgattc cacagtcttc 360
 tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
 tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480
 gcgaatttag tag 493

<210> 451
 <211> 501
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(501)
 <223> n = A,T,C or G

<400> 451
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 ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120
 aacgccaggg ttttccagc cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180
 tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240
 gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300
 tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacia 360
 cgcncacagc actcacagct actcaggagg ctgagaacag gttgaacctg ggagggtggag 420

gttgcaatga gctgagatca ggccnctgcn ccccgatg gatgacagag tgaaactcca 480
tcttaaaaaa aaaaaaaaaa a 501

<210> 452
<211> 51
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(51)
<223> n = A,T,C or G

<400> 452
agacgggttc accnttataa cnccttttag gatgggnntt ggggagcaag c 51

<210> 453
<211> 317
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(317)
<223> n = A,T,C or G

<400> 453
tacctcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60
acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatgggtc tcagaacccat 120
ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc totacatgca 180
taacaaaccc tgtccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccacaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
tacctatgct tttatta 317

<210> 454
<211> 231
<212> DNA
<213> Homo sapiens

<400> 454
ttcgaggtac aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60
taagccacgc cagctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180
ccttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t 231

<210> 455
<211> 231
<212> DNA
<213> Homo sapiens

<400> 455
taccaaagag ggcataataa tcagtctcac agtaggggtc accatcctcc aagtgaaaaa 60
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact totccaagga tcttcctttg gcatcgacca cattcagggg 180
caaagaattt ctcatagcac agtcacaaat acagggtctc tttctcctct a 231

<210> 456
<211> 231

<212> DNA

<213> Homo sapiens

<400> 456

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ttggcaggta cccttacaaa gaagacacca taccttatgc gttattaggt ggaataatca 60
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tgcactcaaa ttccctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tgggtgcagct gctagtcagt ccctgactga cattgccaag t 231
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<210> 457

<211> 231

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(231)

<223> n = A,T,C or G

<400> 457

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gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120
tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g 231
```

<210> 458

<211> 231

<212> DNA

<213> Homo sapiens

<400> 458

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acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t 231
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<210> 459

<211> 231

<212> DNA

<213> Homo sapiens

<400> 459

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ggtaccgagg ctcgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60
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gccctgcact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231
```

<210> 460

<211> 231

<212> DNA

<213> Homo sapiens

<400> 460

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gcaggtataa catgctgcaa caacagatgt gactaggaac ggccggtgac atggggaggg 60
cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a 231
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<210> 461
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 461
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 gtggggttca gtgaggagtg ggaaattggg tcagcagaac caagccgttg ggtgaataag 180
 agggggattc catggcactg atagagccct atagtttcag agctgggaat t 231

<210> 462
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 462
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 gaagaactgt tagagagacc aacagggttag tgggttagag atttccagag tcttacattt 180
 tctagaggag gtatttaatt tcttctcact catccagtgt tgtatttagg a 231

<210> 463
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 463
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<210> 464
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 464
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 ggtgccagcg caccagctag atgctctgta acttctaggc cccattttcc c 231

<210> 465
 <211> 231
 <212> DNA
 <213> Homo sapiens

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 aggatggcac aatttttgct tgtgttcata atatactcag attagttcag ctccatcaga 180
 taaactggag acatgcagga cattagggtg gtgtttagc tctggtaatg a 231

<210> 466
 <211> 231
 <212> DNA

<213> Homo sapiens

<400> 466

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cctgtgcaat	caaataattgt	ggagaattcc	ctagctggag	aagtcacaaa	gactataggg	180
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<210> 467

<211> 311

<212> DNA

<213> Homo sapiens

<400> 467

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<210> 468

<211> 3112

<212> DNA

<213> Homo sapiens

<400> 468

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1:58

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<211> 2229

<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA
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<400> 471

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<210> 474

<211> 1594

<212> DNA

<213> Homo sapiens

<400> 474

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aaaatataaa tatatagaca tctcagataa tatatttgaa atagcaaatt cctgttagaa 180
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<210> 475

<211> 2414

<212> DNA

<213> Homo sapiens

<220>

<221> unsure

<222> (33)

<223> n=A, T, C or G

<400> 475

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aaaaaaaaaa	aaaa					2414

<210> 476
<211> 3434
<212> DNA
<213> Homo sapiens

<400> 476

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<210> 477
<211> 140
<212> PRT
<213> Homo sapiens
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<400> 477																	
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His	Tyr	His	Arg	Asp	Thr	Asp	Thr	Arg	Arg	His	His	His	Met	Asp	Thr		
			20					25					30				
Leu	Ser	His	Tyr	His	Arg	Asp	Thr	Arg	His	His	Thr	Val	Thr	Trp	Thr		
		35					40					45					
His	His	His	Thr	His	Glu	His	Thr	Asp	Thr	Leu	Pro	Tyr	Gly	His	Trp		
	50					55					60						
His	Thr	His	Cys	His	Thr	Val	Thr	Trp	Thr	His	Leu	His	Thr	Ile	Thr		
65					70					75					80		
Pro	Pro	His	Thr	Leu	Pro	Val	Asp	Thr	Arg	Thr	His	Arg	His	Cys	His		
				85					90					95			
Thr	Asp	Thr	Gln	Asn	Thr	Val	Thr	Arg	Arg	His	His	His	Ala	Asp	Thr		
			100					105					110				
Pro	Pro	Leu	Trp	Cys	Arg	Leu	Asn	Tyr	Pro	Ala	Gly	Gly	Thr	Ala	Val		
		115					120					125					
Ala	Tyr	Ser	Cys	Leu	Ser	Asp	Trp	Leu	Ser	Pro	Gln						
130						135					140						

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<210> 478
<211> 143
<212> PRT
<213> Homo sapiens
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<400> 478
Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
                    5                      10                      15

Ser His Gly His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
                    20                      25                      30

Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr
                    35                      40                      45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr

```

50 55 60
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr
 65 70 75 80
 Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser
 85 90 95
 His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp
 100 105 110
 Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser
 115 120 125
 His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val
 130 135 140

<210> 479

<211> 222

<212> PRT

<213> Homo sapiens

<400> 479

Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
 5 10 15
 Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
 20 25 30
 Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr
 35 40 45
 His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr
 50 55 60
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr
 65 70 75 80
 Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser
 85 90 95
 His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val
 100 105 110
 Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val
 115 120 125
 Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr
 130 135 140
 Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His
 145 150 155 160
 Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala
 165 170 175
 Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp

180							185				190				
Thr	Tyr	Ser	Glu	Gly	Lys	Ile	Phe	Phe	Tyr	Phe	Leu	Gly	Asn	Gln	Ala
		195					200					205			
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	210					215					220				

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<210> 480
<211> 144
<212> PRT
<213> Homo sapiens
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<400> 480																	
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				5					10					15			
Cys	Cys	Leu	Trp	Gly	Leu	Gln	Ser	Leu	Pro	Gln	Gly	Ser	Tyr	Val	Thr		
			20					25					30				
Val	Gly	Phe	Leu	Val	Val	Lys	Arg	Gln	Thr	Ile	Gly	Arg	Leu	Glu	Arg		
		35					40					45					
Asp	Phe	Met	Phe	Lys	Cys	Arg	Lys	Gln	Pro	Gly	Leu	Pro	Pro	Ser	Gly		
	50					55					60						
Leu	Cys	Leu	Leu	Trp	Pro	Trp	Pro	Asn	Leu	Glu	Phe	Gly	Arg	Arg	Gln		
	65				70					75					80		
Asp	Arg	Leu	Thr	Trp	Ser	Ser	Val	Ser	Val	Ala	Gly	Val	Cys	Ala	Cys		
				85					90					95			
Arg	Ala	Arg	Pro	Gly	Trp	Leu	Gly	Glu	Gln	Pro	Ala	Thr	Ser	Ala	Gly		
			100					105					110				
Val	Arg	Leu	Glu	Gln	Val	Glu	Gln	Pro	Pro	Ala	His	Pro	Leu	Gln	Glu		
		115					120					125					
Ala	Gly	Val	Ala	Arg	Phe	Pro	Arg	Pro	Glu	Trp	Val	Pro	Pro	Asn	Gly		
	130					135					140						

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<210> 481
<211> 167
<212> PRT
<213> Homo sapiens
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<400> 481
Met His Gly Pro Gln Val Leu Ala Arg Cys Ser Glu Cys Ala Cys Pro
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Ala Leu Ala Ala Thr Ser Ala Gly Val Arg Leu Glu Gly Val Asp Arg
20 25 30

Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys Ser His Ser
 35 40 45
 Leu Ser Gly Cys His Leu Met Ala Asp Gly Ala Lys Ala Leu Gly Lys
 50 55 60
 Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr Asp Val Pro
 65 70 75 80
 Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg
 85 90 95
 Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala
 100 105 110
 Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys Trp Ser His
 115 120 125
 Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe
 130 135 140
 Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser
 145 150 155 160
 Trp Leu Ser Arg Gly Arg Pro
 165

<210> 482
 <211> 143
 <212> PRT
 <213> Homo sapiens

<400> 482
 Met Glu Pro Tyr Arg Gly Asn Lys Lys Gln Val Gln Glu Lys Gly Val
 5 10 15
 Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu
 20 25 30
 Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg
 35 40 45
 Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly
 50 55 60
 Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe
 65 70 75 80
 Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr
 85 90 95
 Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly
 100 105 110
 Ala Ser Gly Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys
 115 120 125

Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly
 130 135 140

<210> 483
 <211> 143
 <212> PRT
 <213> Homo sapiens

<400> 483
 Met Glu Thr Gln Arg Gly Asn Lys Gln Arg Ala Gln Glu Gln Gly Val
 5 10 15
 Cys Cys Leu Trp Gly Ser Ser Pro Cys Leu Gly Ser Tyr Gly Thr Ala
 20 25 30
 Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp
 35 40 45
 Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu
 50 55 60
 Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp
 65 70 75 80
 Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg
 85 90 95
 Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val
 100 105 110
 Arg Leu Val Gln Ala Glu His Pro Pro Pro His Pro Leu Glu Glu Val
 115 120 125
 Gly Met Ala Arg Phe Pro Gln Pro Glu Cys Leu Pro Pro Tyr Cys
 130 135 140

<210> 484
 <211> 30
 <212> PRT
 <213> Homo Sapien

<400> 484
 Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
 1 5 10 15
 Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile
 20 25 30

<210> 485
 <211> 31
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 485
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<210> 486
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 486
 gcgaattctc acgctgagta tttggcc

27

<210> 487
 <211> 36
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 487
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36

<210> 488
 <211> 33
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 488
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33

<210> 489
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 489
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 1 5 10 15
 Ser Val Ala

<210> 490
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 490
 Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys

15

<220>
<223> Made in a lab

<220>
<223> Made in a lab

<220>
<223> Made in a lab

<220>
<223> Made in a lab

<400> 494
Leu Pro Lys Tyr Arg Gly Asp Thr Gly Gly Ala Ser S r Glu Asp Ser
1 5 10 15
Leu Met Ile Ser

20

<210> 495
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 495
 Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro
 1 5 10 15
 Phe Pro Asn Gly
 20

<210> 496
 <211> 21
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 496
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu
 1 5 10 15
 Pro Pro Pro Pro Ala
 20

<210> 497
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 497
 Leu Leu Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val
 1 5 10 15
 Ser Val Arg Val
 20

<210> 498
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 498
 Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val
 1 5 10 15
 Val Pro Gly Arg
 20

<210> 499
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 499
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
 1 5 10 15
 Ser Ala Phe Leu
 20

<210> 500
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 500
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met
 1 5 10 15
 Gly Ser Ile Val
 20

<210> 501
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 501
 Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met
 1 5 10 15
 Val Ser Ala Ala
 20

<210> 502
 <211> 414
 <212> DNA
 <213> Homo Sapien

<220>
 <221> misc_feature
 <222> (1)...(414)
 <223> n=A,T,C or G

<400> 502
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 tcagtcggtg gaggagtccg ggggtcgcct ggtcacgcct gggacacctt tgacantcac 120
 ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180
 agggaagggg ctggaatgga tcggagccat tgataattgt ccacantacg cgacctgggc 240

gaaaggccga ttatnatntt ccaaaacctn gaccacgggtg gatttgaaaa tgaccagtcc 300
 gacaaccgag gacacggcca cctatttttg tggcagaatg aatactggta atagtgggtg 360
 gaagaatatt tggggcccag gcaccctggt caccgtntcc tcagggcaac ctaa 414

<210> 503
 <211> 379
 <212> DNA
 <213> Homo Sapien

<220>
 <221> misc_feature
 <222> (1)...(379)
 <223> n=A,T,C or G

<400> 503
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 agctatggag tgagctgggt ccgccaggct ccagggaagg ggctgggnata catcggatca 180
 ttagtagtag tggtagattt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240
 cctngaccac ggtggatttg aaaatcacca gtttgacaac cgaggacacg gccacctatt 300
 tntgtgccag aggggggttt aattataaag acatttgggg cccaggcacc ctggtcaccg 360
 tntccttagg gcaacctaa 379

<210> 504
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 504
 Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
 1 5 10 15
 Asn Ser Ala

<210> 505
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 505
 Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
 1 5 10 15
 Asn Thr Ala Asn
 20

<210> 506
 <211> 407
 <212> DNA
 <213> Homo Sapien

<400> 506

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accgtctctg	gattctccct	cagtagcaat	gcaatgatct	gggtccgcca	ggctccaggg	180
aaggggctgg	aatacatcgg	atacattagt	tatgggtgta	gcgcatacta	cgcgagctgg	240
gtgaaaggcc	gattcaccat	ctccaaaacc	tcgaccacgg	tggatctgag	aatgaccagt	300
ctgacaaccg	aggacacggc	cacctatttc	tgtgccagaa	atagtgattt	tagtggtatg	360
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<210> 507
 <211> 422
 <212> DNA
 <213> Homo Sapien

<400> 507						
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acagtctctg	gattctccct	cagcaactac	gacctgaact	gggtccgcca	ggctccaggg	180
aaggggctgg	aatggatcgg	gatcattaat	tatgttggtg	ggacggacta	cgcgaaactg	240
gcaaaaggcc	ggttcaccat	ctccaaaacc	tcgaccacgg	tggatctcaa	gatcgccagt	300
ccgacaaccg	aggacacggc	cacctatttc	tgtgccagag	ggtggaagtg	cgatgagctt	360
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aa						422

<210> 508
 <211> 411
 <212> DNA
 <213> Homo Sapien

<220>
 <221> misc_feature
 <222> (1)...(411)
 <223> n=A,T,C or G

<400> 508						
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cagtctctgg	aatcgacctc	agtagctact	gcatgagctg	gggtccgcca	gctccagggg	180
aggggctgga	atggatcgga	atcattggta	ctcctgggtg	cacatactac	gcgaggtggg	240
cgaaaggccg	attcaccatc	tccaaaacct	cgaccacggg	gcatntgaaa	atcnccagtc	300
cgacaaccga	ggacacggcc	acctatttct	gtgccagaga	tcttcgggat	ggtagtagta	360
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<210> 509
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 509	
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser	
1	5 10 15

<210> 510
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Made in a lab

<400> 510

Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile
1				5					10				15	

<210> 511

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 511

Tyr	His	Pro	Ser	Met	Phe	Cys	Ala	Gly	Gly	Gly	Gln	Asp	Gln	Lys
1				5					10				15	

<210> 512

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 512

Asp	Ser	Gly	Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu
1				5					10				15	

<210> 513

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 513

Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Asx	Val	Tyr	Thr	Asn	Leu
1				5					10				15	

<210> 514

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Made in a lab

<400> 514

Leu	Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser
1				5					10				15	

<210> 515

<211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 515
 Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg
 1 5 10 15

<210> 516
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 516
 Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln
 1 5 10 15

<210> 517
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 517
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met
 1 5 10 15

<210> 518
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 518
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
 1 5 10 15

<210> 519
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 519
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys
 1 5 10 15

Gly

<210> 520
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 520
Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr
1 5 10 15
Glu Ala Arg Arg His Tyr Asp Glu Gly
20 25

<210> 521
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 521
Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu
1 5 10 15
Pro Pro Pro Pro Ala
20

<210> 522
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 522
Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp
1 5 10 15
Phe Thr Gln Val
20

<210> 523
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<220>
<221> VARIANT
<222> (1)...(254)
<223> Xaa = any amino acid

<400> 523

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Leu	Gly	Val	Ala	Gly	Ser	Leu	Val	Ser	Gly	Ser	Cys	Ser	Gln	Ile	Ile
			20					25					30		
Asn	Gly	Glu	Asp	Cys	Ser	Pro	His	Ser	Gln	Pro	Trp	Gln	Ala	Ala	Leu
		35					40					45			
Val	Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln
	50					55					60				
Trp	Val	Leu	Ser	Ala	Thr	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly
65					70				75					80	
Leu	Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met
			85					90						95	
Val	Glu	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu
			100					105					110		
Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile	Lys	Leu	Asp	Glu	Ser	Val	Ser	Glu
		115					120					125			
Ser	Asp	Thr	Ile	Arg	Ser	Ile	Ser	Ile	Ala	Ser	Gln	Cys	Pro	Thr	Ala
	130					135					140				
Gly	Asn	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly	Leu	Leu	Ala	Asn	Gly	Arg
145				150						155				160	
Met	Pro	Thr	Val	Leu	Gln	Cys	Val	Asn	Val	Ser	Val	Val	Ser	Glu	Glu
			165					170						175	
Val	Cys	Ser	Lys	Leu	Tyr	Asp	Pro	Leu	Tyr	His	Pro	Ser	Met	Phe	Cys
		180						185					190		
Ala	Gly	Gly	Gly	Gln	Xaa	Gln	Xaa	Asp	Ser	Cys	Asn	Gly	Asp	Ser	Gly
		195					200					205			
Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu	Val	Ser	Phe	Gly
	210					215					220				
Lys	Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Gly	Val	Tyr	Thr	Asn	Leu
225					230					235				240	
Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser		
				245						250					

<210> 524

<211> 765

<212> DNA

<213> Homo sapien

<400> 524

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tcgcagccct	ggcaggcggc	actggtcctg	gaaaacgaat	tggtctgctc	gggcgtcctg	180
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aagttggacg	aatccgtgtc	cgagtctgac	accatccgga	gcacgagcat	tgcttcgcag	420
tgccctaccg	cggggaactc	ttgcctcggt	tctggctggg	gtctgctggc	gaacggcaga	480
atgcctaccg	tgctgcagtg	cgtgaacgtg	tccggtgggt	ctgaggaggt	ctgcagtaag	540
ctctatgacc	cgctgtacca	ccccagcatg	ttctgcgccg	gcccagggca	agaccagaag	600
gactcctgca	acggtgactc	tggggggccc	ctgatctgca	acgggtactt	gcagggcctt	660
gtgtctttcg	gaaaagcccc	gtgtggccaa	gttggcgtgc	caggtgtcta	caccaacctc	720
tgcaaattca	ctgagtggat	agagaaaacc	gtccaggcca	gttaa		765

<210> 525

<211> 254

<212> PRT

<213> Homo sapien

<400> 525

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Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
 1          5          10          15
Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
 20          25          30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
 35          40          45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
 50          55          60
Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
 65          70          75          80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
 85          90          95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
100          105          110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
115          120          125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
130          135          140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145          150          155          160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
165          170          175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
180          185          190
Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
195          200          205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
210          215          220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225          230          235          240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
245          250

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<210> 526

<211> 963

<212> DNA

<213> Homo sapiens

<400> 526

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aactgcatcg tggcttccat cgtaaggacg gaacgcagcc tgcacgctcc gatgtacctc 180
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<210> 527

<211> 320

<212> PRT

<213> Homo sapiens

<400> 527

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Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser
 20 25 30

Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val
 35 40 45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met
 50 55 60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile
 65 70 75 80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys
 85 90 95

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr
 100 105 110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro
 115 120 125

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly
 130 135 140

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu
 145 150 155 160

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser
 165 170 175

Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu
 180 185 190

Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val
 195 200 205

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val
 210 215 220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys
 225 230 235 240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro L u Ile Gly
 245 250 255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg
 260 265 270

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala
290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys
305 310 315 320

<210> 528
<211> 20
<212> DNA
<213> Homo Sapien

<400> 528
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20

<210> 529
<211> 20
<212> DNA
<213> Homo Sapien

<400> 529
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20

<210> 530
<211> 1852
<212> DNA
<213> Homo sapiens

<400> 530
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tgtgtctgtt gagatgctta tgtgactttg cttttaattc tgtttatgtg attatcacat 240
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ctgcggcagc ttccgggataa cttgaggctg catcactggg gaagaaacac aytctgtgcc 360
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gctttctcca ccttgctgga agtgacctgc tgtccagaag tttgatggct gaggagtata 720
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<210> 531
<211> 879
<212> DNA
<213> Homo sapiens

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<210> 532
<211> 292
<212> PRT
<213> Homo sapiens
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<400> 532

Met	His	Leu	Ser	Phe	Pro	Ala	Phe	Leu	Pro	Pro	Trp	Met	Asp	Arg	Gly
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Ser	Gly	Lys	Ser	Asn	Val	Gly	Thr	Ser	Gly	Asp	His	Asn	Asp	Ser	Ser
			20					25					30		
Val	Lys	Thr	Leu	Gly	Ser	Lys	Arg	Cys	Lys	Trp	Cys	Cys	His	Cys	Phe
		35					40					45			
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Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Ile His Glu		
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Cys Arg Lys Gln Pro Gly Ser Pro Ser Arg Gly Leu Gly Leu Leu Trp
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 Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala Gln Lys Pro Ser Leu
 65 70 75 80
 Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser Tyr Leu Val Leu Gly
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 Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val Ile Gln Pro Ile Phe
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 Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr Asp Pro Met Asp Ser
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 Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr Val Leu Thr Phe Cys
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 Thr Thr Tyr Val Leu Leu Gly Ser Val Ile Thr Ala Ser Arg Val Phe

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Gln Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr		
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 Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile Cys Ala Met Phe Val
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<210> 553

<211> 58

<212> PRT

<213> Homo sapiens

<400> 553

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Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
      20                                25                                30

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Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
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Glu Pro His His Thr Gly Gly Gly Glu His
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<210> 554

<211> 59

<212> PRT

<213> Homo sapiens

<400> 554

Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile
 5 10 15

Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val
 20 25 30

Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro
 35 40 45

Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu
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<210> 555

<211> 71

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<213> Homo sapiens

<400> 555

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Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser
 20 25 30

Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp
 35 40 45

Leu Val Ala Lys Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro
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Ser Asp Pro Leu Glu Leu Leu
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<210> 556

<211> 81

<212> PRT

<213> Homo sapiens

<400> 556

Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr
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Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr
 20 25 30

Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly
 35 40 45

Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile

<210> 557.
<211> 54
<212> PRT
<213> Homo sapiens

Gly Phe His Ile Arg Phe
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<210> 558
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<213> Homo sapiens
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<220>  
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<222> (1)...(77)  
<223> Xaa = Any amino acid
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Pro Ser Tyr Leu Ser Gly Val Leu His Ser Arg Ser Tyr
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<210>	559
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204

<213> Homo sapiens

<400> 559

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Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala
 20 25 30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala
 35 40 45

Pro Arg
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<210> 560

<211> 56

<212> PRT

<213> Homo sapiens

<400> 560

Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly
 5 10 15

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr
 20 25 30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn
 35 40 45

Thr Asp Leu Phe Leu Pro Pro Leu
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<210> 561

<211> 57

<212> PRT

<213> Homo sapiens

<220>

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<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 561

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 5 10 15

Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser
 20 25 30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn
 35 40 45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn
 50 55

205

<210> 562
<211> 59
<212> PRT
<213> Homo sapiens

<220>
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<222> (1)...(59)
<223> Xaa = Any amino acid

<400> 562
Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val
 5 10 15

Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu
 20 25 30

Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val
 35 40 45

Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro
 50 55

<210> 563
<211> 79
<212> PRT
<213> Homo sapiens

<400> 563
Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro
 5 10 15

Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His
 20 25 30

Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met
 35 40 45

Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg
 50 55 60

Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg
 65 70 75

<210> 564
<211> 64
<212> PRT
<213> Homo sapiens

<400> 564
Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala
 5 10 15

Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr
 20 25 30

Val Arg His Leu Tyr Il Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser
 35 40 45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro
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<210> 565

<211> 57

<212> PRT

<213> Homo sapiens

<220>

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<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 565

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 5 10 15

Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln
 20 25 30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu
 35 40 45

Tyr Ala Val Ser Ser Xaa His Asn Val
 50 55

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg
 5 10 15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His
 20 25 30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro
 35 40 45

Leu Lys Leu Val Leu Leu Pro
 50 55

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu

5 10 15
 Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile
 20 25 30
 Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile
 35 40 45
 Phe Arg Thr
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<210> 568
 <211> 75
 <212> PRT
 <213> Homo sapiens

<400> 568
 Lys Val Gly Glu Tyr Ile Leu Gln Ser Leu Leu Arg Ile Arg Lys Ile
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 Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu
 20 25 30
 Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr
 35 40 45
 Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp
 50 55 60
 Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu
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<210> 569
 <211> 4809
 <212> DNA
 <213> Homo sapiens

<400> 569
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<210> 570

<211> 951

<212> DNA

<213> Homo sapiens

<400> 570

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<210> 571

<211> 819

<212> DNA

<213> Homo sapiens

<400> 571

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<210> 572

<211> 203

<212> DNA

<213> Homo sapiens

<400> 572

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<210> 573
<211> 132
<212> PRT
<213> Homo sapiens
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Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg
      20              25              30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
      35              40              45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
      50              55              60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
      65              70              75              80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
      85              90              95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
      100              105              110

Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
      115              120              125

Leu Leu Asn Tyr
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<210> 574
<211> 62
<212> PRT
<213> Homo sapiens
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<400> 574
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His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
20 25 30
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35 40 45
Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
50 55 60

<210> 575

211

<211> 76
 <212> PRT
 <213> Homo sapiens

<400> 575
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 50 55 60
 Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys
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<210> 576
 <211> 68
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (1)...(68)
 <223> Xaa = Any Amino Acid

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 Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln
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 Pro Gly Tyr Ser
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<210> 577
 <211> 57
 <212> PRT
 <213> Homo sapiens

<400> 577
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 Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro

212

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Arg Leu Ala Pro Pro Ala Asp Thr Pro
 50 55

<210> 578

<211> 51

<212> PRT

<213> Homo sapiens

<400> 578

Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His
 5 10 15

His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr
 20 25 30

Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr
 35 40 45

Gln Pro His
 50

<210> 579

<211> 56

<212> PRT

<213> Homo sapiens

<400> 579

Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu
 5 10 15

Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr
 20 25 30

Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His
 35 40 45

Ile Ala Lys Val Tyr Gln Pro His
 50 55

<210> 580

<211> 67

<212> PRT

<213> Homo sapiens

<400> 580

Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser
 5 10 15

Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys
 20 25 30

Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser
 35 40 45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser
 50 55 60

Phe Ile His
 65

<210> 581

<211> 77

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu
 5 10 15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser
 20 25 30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala
 35 40 45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu
 50 55 60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser
 65 70 75

<210> 582

<211> 51

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile
 5 10 15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val
 20 25 30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe
 35 40 45

Leu Gly Val
 50

<210> 583

<211> 60

<212> PRT

<213> Homo sapiens

<400> 583

214

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
5 10 15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
20 25 30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
35 40 45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
50 55 60

<210> 584

<211> 76

<212> PRT

<213> Homo sapiens

<400> 584

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
35 40 45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
65 70 75

<210> 585

<211> 50

<212> PRT

<213> Homo sapiens

<400> 585

Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu
5 10 15

Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp
20 25 30

Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu
35 40 45

Leu Phe
50

<210> 586

<211> 60

<212> PRT

<213> Homo sapiens

<400>	587						
ctggacactt	tgcgagggct	tttgcctggct	gctgctgctg	cccgatcatgc	tactcatcgt	60	
agcccgcccg	gtgaagctcg	ctgctttccc	tacctcctta	agtgaactgcc	aaacgcccac	120	
cggctggaat	tgctctgggt	atgatgacag	agaaaatgat	ctcttcctct	gtgacaccaa	180	
cacctgtaaa	tttgatgggg	aatgtttaag	aattggagac	actgtgactt	gctctgtca	240	
gttcaagtgc	aacaatgact	atgtgcctgt	gtgtggctcc	aatggggaga	gctaccagaa	300	
tgagtgtta	ctgcgacagg	ctgcatgcaa	acagcagagt	gagactactg	tggtgtcaga	360	
aggatcatgt	gccacagatg	caggatcagg	atctggagat	ggagtccatg	aaggctctgg	420	
agaaactagt	caaaaaggaga	catccacctg	tgatatttgc	cagtttggtg	cagaatgtga	480	
cgaagatgcc	gaggatgtct	ggtgtgtgtg	taatattgac	tgttctcaaa	ccaacttcaa	540	
tcccctctgc	gcttctgatg	ggaaatctta	tgataatgca	tgccaaatca	aagaagcatc	600	
gtgtcagaaa	caggagaaaa	ttgaagtcat	gtctttgggt	cgatgtcaag	ataacacaac	660	
tacaactact	aagtctgaag	atgggcatta	tgcaagaaca	gattatgcag	agaatgctaa	720	
caaattagaa	gaaagtgcc	gagaacacca	cataccttgt	ccggaacatt	acaatggctt	780	
ctgcatgcat	gggaagtgtg	agcattctat	caatatgcag	gagccatctt	gcaggtgtga	840	
tgctggttat	actggacaac	actgtgaaaa	aaaggactac	agtgttctat	acgttgttcc	900	
cggctcctgta	cgatttccagt	atgtcttaat	cgcagctgtg	attggaacaa	ttcagattgc	960	
tgatcatctgt	gtggtggtcc	tctgcatcac	aaggaaatgc	cccagaagca	acagaattca	1020	
cagacagaag	caaaatacag	ggcactacag	ttcagacaat	acaacaagag	cgtccacgag	1080	
gttaatctaa	agggagcatg	tttcacagtg	gctggactac	cgagagcttg	gactacacaa	1140	
tacagtatta	tagacaaaag	aataagacaa	gagatctaca	catgtgtcct	tgcatattgtg	1200	
gtaatctaca	ccaatgaaaa	catgtactac	agctatatatt	gattatgtat	ggatatattt	1260	
gaaatagtat	acattgtctt	gatgtttttt	ctgtaatgta	aataaactat	ttatatcaca	1320	
caatawagtt	ttttctttcc	catgtatttg	ttatatataa	taaataactca	gtgatgagaa	1380	
aaaaaaaaaa	aaaaaaaaaa	rwmgaccc				1408	

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<400> 588
Met Pro Gln Lys Gln Gln Asn Ser Gln Thr Glu Ala Lys Tyr Arg Ala
                    5                      10                      15

Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys
                20                      25                      30

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216

Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln
 35 40 45
 Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys
 50 55 60
 Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr
 65 70 75 80
 Ile

<210> 589
 <211> P57
 <212> PRT
 <213> Homo sapiens

<400> 589
 Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met
 5 10 15
 Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu
 20 25 30
 Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu
 35 40 45
 Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro
 50 55 60
 Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg
 65 70 75 80
 Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile
 85 90 95
 Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser
 100 105 110
 Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp
 115 120 125
 Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly
 130 135 140
 Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn
 145 150 155

<210> 590
 <211> 347
 <212> PRT
 <213> Homo sapiens

<400> 590
 Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr
 5 10 15

Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr
 20 25 30
 Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys
 35 40 45
 Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys
 50 55 60
 Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly
 65 70 75 80
 Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln
 85 90 95
 Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala
 100 105 110
 Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser
 115 120 125
 Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys
 130 135 140
 Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser
 145 150 155 160
 Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp
 165 170 175
 Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile
 180 185 190
 Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr
 195 200 205
 Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala
 210 215 220
 Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu
 225 230 235 240
 His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn
 245 250 255
 Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His
 260 265 270
 Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val
 275 280 285
 Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile
 290 295 300
 Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg
 305 310 315 320

Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser
 325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile
 340 345

<210> 591
 <211> 565
 <212> DNA
 <213> Homo sapien

<400> 591
 actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa 60
 cttcatgctt tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg 120
 aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact 180
 caggaagcaa gagttaatcc cagaggtcta tgcctaatag tgttatggca aatggatgtc 240
 atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagttga tacttattca 300
 catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta 360
 ttatcttgtt ttcctgtcat gggagttcca gaaaaagtta aaacagacaa tgggccagggt 420
 tactgtagta aagcatttca aaaattctta aatcagtggg aaattacaca tacaatagga 480
 attctctata attcccaagg acaggccata attgaaggaa ctaatagaac actcaaagct 540
 caattggta aacaaaaaaa aaaaa 565

<210> 592
 <211> 188
 <212> PRT
 <213> Homo sapien

<400> 592
 Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile
 1 5 10 15
 Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu
 20 25 30
 Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln
 35 40 45
 His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg
 50 55 60
 Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val
 65 70 75 80
 Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val
 85 90 95
 Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser
 100 105 110
 Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly
 115 120 125
 Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys
 130 135 140
 Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly
 145 150 155 160
 Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg
 165 170 175
 Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys
 180 185

<210> 593
 <211> 271

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(271)
<223> n = A,T,C or G

<400> 593
actttatggt cnagtgcana aancncctg gattgccacc ntactctcag ggctgtgant 60
tgtgcnccca nagcaacctg ggcaacgagg gacagggggg ccnacaattg agggagcggg 120
gtccctagct ggggtctata catgncnggg naagggcngc tgagtnccat nagcaaagga 180
nctagnatnt gcgggggtgc ggctggggc taccctttna agcatccntn gatccactcc 240
angaancgng gggtagncag gtttnccaac a 271

<210> 594
<211> 376
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(376)
<223> n = A,T,C or G

<400> 594
cctttggggg nggggggaac ctttaccatt gtncaccttt atttcatttg gttnggggttc 60
gcgcctcnnn gggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc 120
cgattaagcg ncaaattgtgt agcaaaangc cgtgccactt gtggcgtagc tncgtcgggt 180
cgattcgacg acaaggcgtn gcgcgntanc gttagtctcn aatngaccn gtggcatgag 240
cccacgangg ntctgtgtcg tcacatggnc tctagacata acgcnccn ttttttncag 300
agggggntgc gcgccttagg gaggnagggg tggggacact agccaancca nantctnacc 360
ccattgaaga aaaggn 376

<210> 595
<211> 242
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(242)
<223> n = A,T,C or G

<400> 595
agnctgctgn tcgtnccctn tatgtggctt catnntgagg acaanagtng cactgagget 60
tgngnatgcc aggcaaggnc aagctggctc aaaaagcacc caccacctc tagnaanggt 120
atgccangag cangtgcacc agtcccaact angagnccn ggcatgntac atcttcttcc 180
accctnaaa ntttngngta caangnccat ttttctttt ctcttaaggg ncnctnggct 240
tc 242

<210> 596
<211> 535
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(535)

<223> n = A,T,C or G

<400> 596

accagttgga	tactgctaaa	nagatattta	tgcagcctca	tatgttaagt	cgtatatttt	60
gaaagctttt	taaatttttt	ctttaagaag	atttttagatg	cttatcaactg	agtaccagag	120
ggatgtaggc	tgatgccctt	atcaacaaag	tcagggactg	tggcacacaa	ggattgacta	180
ctgcagacac	ggccacaatg	ctacctctag	agggcctgaa	tccccctgcc	ctctctggtg	240
gggagaaggg	ctggcagagc	cattagcatg	ggctccggcc	aatcctggcc	actttgacac	300
tcctggtgct	gacctagggt	cctggaggaa	gggatgaggt	gggcagtaga	gatgctcagg	360
gcagtggccc	ctttccatcc	acactggaac	tatttcagta	ttttaccacc	aattcagcca	420
ttcccttggtg	cgtctggtga	acatcagccc	tgctccaggt	ctcagtttcc	cctttgtaaa	480
gggaaagctc	tggattcagg	gagtgatgaa	gaggtcatca	tggctctgag	aattc	535

<210> 597

<211> 257

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(257)

<223> n = A,T,C or G

<400> 597

tttcnatacc	caaaantacc	ccatattang	accanacatt	tgtctnggaa	aaattaccat	60
tntntaactn	ttgggccacc	tgagannaaa	tggtgtgaat	ncatgataag	atggancagn	120
attnctctta	agatnngatn	agaccccggt	tttcacggaa	catatccaag	nacccaatag	180
gnaacaagcc	acggngggag	tcacaaacat	atattcttta	ctctcataat	ccgtnncaca	240
naactnttgn	acttgac					257

<210> 598

<211> 222

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(222)

<223> n = A,T,C or G

<400> 598

nntggntacc	gtcnaaaactt	nncttggtac	ccgagctcgg	atccactagt	ccagtgtggt	60
ggaattccat	tgtgttgggc	tataagctgt	aatagtggag	ncgtgctnng	ttcattgcan	120
nagnccctcc	gcanncacnc	ttggnacaac	ctgtgagnag	gcnataaatt	attcacataa	180
tcatcactgc	atgaantcga	ctcaaacgca	tccacntaca	cc		222

<210> 599

<211> 238

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(238)

<223> n = A,T,C or G

<400> 599

gcatgacatc	ancgatgtnt	ttggnnacct	ganattngct	aaaactngng	natgccgggn	60
atgnagggtt	ggtantgatc	tatgcaactc	catctcatgg	ggacgtttca	tgtggagtgn	120
tcgacaangt	tgctgnancn	gagaagtgat	gatctcagtt	gaaagggtca	tgtgaatata	180
cnttacactt	gaaaaagaag	cacattggga	atatcacgaa	acgnccacca	acatcctg	238

<210> 600

<211> 232

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(232)

<223> n = A,T,C or G

<400> 600

cgaactat	ttt	agactaccta	ggaaaattat	tttagtatca	gaagaatatc	aggggtgtag	60
tactcatcag	agctaaatga	gagcgcttta	aaaatgttag	tttgtcttcc	gccatttcta		120
cagaaagctg	caatttcagg	ttttcaacct	aatagggtgat	atttaanaaa	aaaaaaaagc		180
aatcgcaa	aat	agccccactg	cttttacaaa	tcattttttc	cccaacacaa	tg	232

<210> 601

<211> 547

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(547)

<223> n = A,T,C or G

<400> 601

cattgtgttg	gggaaaaaat	gatttgtata	agcagtgggg	ctatttgcca	ttgctttttt	60
tttttcttaa	atatcaccta	ttaggttgaa	aacctgaaat	tgcagctttc	tgtagaaatg	120
gcggaagaca	aactaacatt	tttaaagcgc	tctcatttag	ctctgatgag	tactacaccc	180
ctnatattct	tctgatacta	aaataatttt	cctagtgtag	tctaaacttt	tttaaaaaga	240
catgtaatcc	gcggagttag	taactcaaaa	cgagtgcac	tnnggaagtat	cgcagccgtt	300
nctggatnaa	attcccagct	tgctngcttg	ctnagccggg	gggctgtnaa	aaaaacatct	360
gcagcccngg	ggnaaaaacc	ttcgcatgtg	tcttacgtgt	ttacgttatt	ttatttccct	420
nnagcaaggc	nggganttgg	ggactcgaaa	tggtacagtt	gggctgggga	tcgcccttgt	480
tacataaaag	ncgtccagaa	gagggacggt	tacaggcngg	ganctccaaa	ggtcagtcct	540
tgccatt						547

<210> 602

<211> 826

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(826)

<223> n = A,T,C or G

<400> 602

cggggggnnt	tacgtctctc	tggaacgttt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttget	ctagggaat	aaaataacgt	aaacacgtaa	120
gaacaatgcg	aaagcgtttt	cttccctagg	ctgcagattg	tcttcttcac	cgcccctgct	180
tagctagcta	gctagctggg	aatttaatcc	agaaacggct	tgcgatacct	cctagatgca	240

ctcgttttga	gttacaaact	ccgcggatta	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaaat	tatttttagta	tcagaagaat	atcaggggggt	gtagtactca	tcagagctna	360
atgagagcgc	tttaaaaatg	ttagtttgtc	ttccgccatt	tctacagaaa	gctgcaattt	420
caggttttca	ncctaatagg	tgatatntaa	gaaaaaaaaa	acaatcgcan	atagcccact	480
gctttttacaa	atcattttttc	tcttctaggt	atagcctgtc	aggtggccta	atgtattttt	540
gacatctcta	ggaatttttaa	tagaccagaa	atgggtgccca	gagatatgcc	tgactaatc	600
ttaagtgggg	atztatgtat	ttctcaanca	agtgattaaa	gcaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aatcatgaa	nanttttana	attattttan	gaatctgtgg	720
cttctcttct	taaaatngaa	aaaaaaattg	tttaaacccta	naaggtctga	atacccaagc	780
ncctgaacn	anagaacaan	gccggagcac	cccctcccaa	atcccc		826

<210> 603

<211> 817

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(817)

<223> n = A,T,C or G

<400> 603

nnangacttt	tgtggtntta	tacaattntt	ttttctattt	ctatgaagag	aaagccacag	60
agtcctaaaa	taattctaaa	actcatcatg	actttcttgc	ctaaaagatc	ttgatttcaa	120
tcgtgcctag	ttttgcttta	atcaacttgc	tgagaaatac	ataaatcccc	acttaagatt	180
agtgaggcca	tatctctggc	acccattttc	ggttctatta	aaattcctag	agatgtcaaa	240
aattacatta	ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgtaaaagca	300
gtggggctat	ttgcgattgc	tttttttttt	tcttaaatat	cacctattag	gttgaaaacc	360
tgaaattgca	gctttctgta	gaaatggcgg	aagacaaaact	aacattttta	aagcgctctc	420
atntagctct	gatgagtact	acacccttga	tattcttctg	atactaaaat	aatttttcta	480
gtgtagtcta	aactttttta	aaaagacatg	taatccgcgg	agtttgtaac	tcaaaacgag	540
tgcatctagg	aggtatcgca	agcggtttct	ggattaaatt	cccagctagc	ttgcttgctt	600
agcagggggc	ggnaaanaag	acatctgcag	cctagggaag	aaaacctttc	gcattgttct	660
tacgtgttta	cgttatttta	tttcctanaa	caaggcngaa	ttgggactcg	aatggttcag	720
ttgggggtgg	ggatcccctg	gtncataaaa	ngtcanaaag	anggtacagg	cggaaaccca	780
agggtcgtcc	tgcatttana	ctcggaattt	tggtgccc			817

<210> 604

<211> 694

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(694)

<223> n = A,T,C or G

<400> 604

cttttcaaact	catttttnct	cttctaggta	tancctgtca	gggtggcctaa	tgtaattttt	60
gacatctcta	ngaatttttaa	tagaaccaga	aatgggtgcc	agagatatgc	ctgcactaat	120
cttaagtggg	gatttatgta	tttctcaagc	aagtgattaa	agcaaaaacta	ggcacgattg	180
aatcaagat	cttttaggca	anaaagtcac	gatgagtttt	agaattattt	taggactctg	240
tggcttttct	ttcatagaaa	tagaaaaaaa	aattgtataa	aaccacaaaa	ggtcctgaat	300
agccaaagca	acactganca	aaaagaacan	agcagggaag	caacacacta	ccngaattca	360
aattatacta	ccagggtgta	gtaacaaaaa	cagcattcta	ttggcataaa	atagacacca	420
agaccaatgg	ancagaataa	agaacccac	aaataaatcc	atatatntac	cgccanctga	480
ttatcaataa	cnaacaccaa	gaacatatnt	taagggaacnt	nctattcaat	aantagtgtc	540
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223

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<211> 678

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<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(678)

<223> n = A,T,C or G

<400> 605

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<211> 263

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(263)

<223> n = A,T,C or G

<400> 606

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agtgancana	cntgtcccca	ctgaggtgcc	ccacagcngn	ttgtnttcag	cangggctna	180
caactcgacc	ggcagcgan	ggctggcaga	antgngcgcc	tnnctcatte	ctacgcngtn	240
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<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 607

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<210> 608

<211> 22

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<223> Primer

<400> 608

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22

<210> 609

<211> 40

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 609

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<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 610

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<223> Primer

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<213> Homo sapien

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<400> 617

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His	Pro	Leu	Tyr	Asp	Met	Ser	Leu	Leu	Lys	Asn	Arg	Phe	Leu	Arg	Pro
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Lys	Phe	Met	Leu	Cys	Ala	Gly	Arg	Trp	Thr	Gly	Gly	Lys	Ser	Trp	Gly
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Ser	Glu	Pro	Cys	Ala	Leu	Pro	Glu	Arg	Pro	S	r	Leu	Tyr	Thr	Lys
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420 425 430
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 <212> DNA
 <213> Homo sapien

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<210> 620

<211> 2051

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(2051)

<223> n = A,T,C or G

<400> 620

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<210> 621

<211> 2841

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(2841)

<223> n = A,T,C or G

<400> 621

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<210> 622

<211> 3228

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(3228)

<223> n = A,T,C or G

<400> 622

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<210> 623

<211> 4894

<212> DNA

<213> Homo sapiens

<400> 623

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<213> Homo sapiens

<400> 627

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Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly
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Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu
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Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly
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Val Ser Gly Lys Gln Leu Trp Arg Met Leu Leu
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Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
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Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro
 50 55 60

Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr
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Leu Cys Pro Gly Ser Cys Leu Glu Gly Glu Val Val Cys Trp Glu Gly
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Ile Ala Gly Gln Glu Gly Asp Pro Gly Leu Arg Gly His Thr Lys Arg
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Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly
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Leu Trp Leu Ala Leu Leu
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 Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu
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 Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val
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 Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala
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 Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe
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<213> Homo sapiens

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Asn Gln Asp Asn Ala Val Ser His His Thr Trp Glu Phe Gln Thr Ser
      20              25              30

Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
      35              40              45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
      50              55              60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
      65              70              75              80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
      85              90              95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
      100             105             110

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
      115             120             125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
      130             135             140

Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
      145             150             155             160

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
      165             170             175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
      180             185             190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
      195             200             205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
      210             215             220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly

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225 230 235 240
 Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr
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 Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala
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 Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser
 275 280 285
 Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val
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 Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His
 305 310 315 320
 Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg
 325 330 335
 Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr
 340 345 350
 Pro Gln Glu Arg Ser Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu
 355 360 365
 Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe
 370 375 380
 Val Phe Ser Glu Val Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met
 385 390 395 400
 Val Asn Gly Gln Glu Glu Leu His Val Ile Ser Met Glu Thr Thr Ser
 405 410 415
 Ile Gly Lys Asn Ile Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg
 420 425 430
 Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg
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 Gln Val Met Asp His Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His
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 Arg Arg Pro Val Lys Glu Asn Phe Leu His Met Ser Val Gln Ser Asp
 465 470 475 480
 Asp Val Leu Leu Gly Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg
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 Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu
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 Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys
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 Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp
 530 535 540

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val
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 Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met
 565 570 575

Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu
 580 585 590

Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile
 595 600 605

Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu
 610 615 620

Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val
 625 630 635 640

Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys
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Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys
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Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys
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<210> 633

<211> 679

<212> PRT

<213> Homo sapiens

<400> 633

Met Met Asp Ala Ser Lys Glu Leu Gln Val Leu His Ile Asp Phe Leu
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 35 40 45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
 50 55 60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
 65 70 75 80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
 85 90 95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
 100 105 110

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
 115 120 125

S r Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
130 135 140

~~Asp Met Val Phe Met Pro Asn Glu Asn Glu Arg Lys Glu Thr Ile Leu~~
~~145 150 155 160~~

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
165 170 175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
180 185 190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
195 200 205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
210 215 220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly
225 230 235 240

Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr
245 250 255

Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala
260 265 270

Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser
275 280 285

Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val
290 295 300

Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His
305 310 315 320

Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg
325 330 335

Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser
340 345 350

Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys
355 360 365

Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val
370 375 380

Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu
385 390 395 400

Glu Leu His Val Il Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile
405 410 415

Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu
420 425 430

Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His

435	440	445
Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His Arg Gln Pro Val Lys		
450	455	460
Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly		
465	470	475
Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu		
	485	490
Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly		
	500	505
Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln		
	515	520
Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile		
	530	535
Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile		
	545	550
Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe		
	565	570
Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly		
	580	585
Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu		
	595	600
Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile		
	610	615
Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr		
	625	630
Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys		
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<210> 634

<211> 5668

<212> DNA

<213> Homo sapiens

<400> 634

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<210> 635

<211> 1095

<212> PRT

<213> Homo sapiens

<400> 635

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Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
          20                      25                      30

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Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
          35                      40                      45

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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
          50                      55                      60

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Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
          65                      70                      75                      80

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```

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
          85                      90                      95

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250

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 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
 115 120 125
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
 130 135 140
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
 145 150 155 160
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
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 Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile
 180 185 190
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
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 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu
 210 215 220
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro
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 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn
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 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu
 260 265 270
 Glu Lys His Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly
 275 280 285
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 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val
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 Glu Gly Ser Gly Arg Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val
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 Glu Asp Ala Pro Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe
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 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val
 370 375 380
 Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser
 385 390 395 400

Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn
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 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val
 485 490 495
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu
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 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val
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 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile
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 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu
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 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu
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 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr
 610 615 620
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu
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 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala

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		995					1000					1005		
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<212> PRT

<213> Homo sapiens

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Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
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Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
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Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
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Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser

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Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn
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 660 665 670
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 690 695 700
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Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr
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 770 775 780
 Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe
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 Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu
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 850 855 860
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 Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys
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 Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu
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 Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile
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tacatcgcgc agtccaaagg tgcttggatt ctacgggag gcacccatta tggcctgatg 540
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gtggccattg gcatagcagc ttggggcatg gtctccaacc gggacaccct catcagggaat 660
tgcgatgctg agggctatct tttagcccag taccttatgg atgacttcac aagagatcca 720
ctgtatatcc tggacaacaa ccacacacat ttgtgtctcg tggacaatgg ctgtcatgga 780
catcccactg tcgaagcaaa gctccggaat cagctagaga agtatatctc tgagcgcaact 840
attcaagatt ccaactatgg tggcaagatc cccatttgtt gttttgcccc aggaggtgga 900
aaagagactt tgaaagccat caatacctcc atcaaaaata aaattccttg tgtgtgtgtg 960
gaaggctcgg gccagatcgc tgatgtgatc gctagcctgg tggaggtgga ggatgccctg 1020
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gctgctgggg agtccgagga gctggctaag gagtacgaga cccgggctgt tgagctgttc 1860
actgagtgtt acagcagcga tgaagacttg gcagaacagc tgctggtcta ttctgtgaa 1920
gcttgggggtg gactcgagca ccaccaccac caccactga 1959

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<210> 675
 <211> 652
 <212> PRT
 <213> Homo sapiens

<400> 675

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
      5                      10                      15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
      20                      25                      30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
      35                      40                      45

Thr Lys Asp S r Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
      50                      55                      60

```

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
 65 70 75 80
 Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
 85 90 95
 Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser
 100 105 110
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
 115 120 125
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
 130 135 140
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
 145 150 155 160
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
 165 170 175
 Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile
 180 185 190
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp
 195 200 205
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu
 210 215 220
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro
 225 230 235 240
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn
 245 250 255
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu
 260 265 270
 Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly
 275 280 285
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu
 290 295 300
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val
 305 310 315 320
 Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val
 325 330 335
 Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe
 340 345 350
 Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp
 355 360 365
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val

370	375	380
Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser		
385	390	395 400
Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn		
	405	410 415
Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu		
	420	425 430
Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp		
	435	440 445
Leu Glu Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe		
	450	455 460
Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr		
	465	470 475 480
His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val		
	485	490 495
Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu		
	500	505 510
Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys		
	515	520 525
Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val		
	530	535 540
Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile		
	545	550 555 560
Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg		
	565	570 575
Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu		
	580	585 590
Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu		
	595	600 605
Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr		
	610	615 620
Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu		
	625	630 635 640
Ala Trp Gly Gly Leu Glu His His His His His His		
	645	650

<210> 676

<211> 132

<212> PRT

<213> Homo sapien

<400> 676

```

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1      5      10      15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20      25      30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35      40      45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50      55      60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65      70      75      80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85      90      95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100     105     110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115     120     125
Gly Pro Pro Ala
130

```

<210> 677

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 677

ggggaattca tgatccggga gaaatttgcc cactgc

36

<210> 678

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 678

gggctcgagt caggagtttg agaccagcct ggc

33

<210> 679

<211> 675

<212> DNA

<213> Homo sapiens

<400> 679

```

atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggttcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

```



```

accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgacacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcgggtga cctggcaaac caagtcgggc 360
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt catgatccgg 420
gagaaatttg cccactgcac cgtgctaacc attgcacaca gattgaacac cattattgac 480
agcgacaaga taatggtttt agattcagga agactgaaag aatatgatga gccgtatgtt 540
ttgctgcaaa ataaagagag cctattttac aagatgggtg aacaactggg caaggcagaa 600
gccgctgccc tcaactgaaac agcaaaacag agatgggggt tcacccatgtt ggccaggctg 660
gtctcaaact cctga 675

```

<210> 680

<211> 291

<212> DNA

<213> Homo sapiens

<400> 680

```

atggggatcc gggagaaaatt tgcccactgc accgtgctaa ccattgcaca cagattgaac 60
accattattg acagcgacaa gataatggtt ttagattcag gaagactgaa agaatatgat 120
gagccgtatg ttttgctgca aaataaagag agcctathtt acaagatggt gcaacaactg 180
ggcaaggcag aagccgctgc cctcactgaa acagcaaaac agagatgggg ttccaccatg 240
ttggccaggc tgggtctcaaa ctccctcgag caccaccacc accaccactg a 291

```

<210> 681

<211> 1074

<212> DNA

<213> Homo sapiens

<400> 681

```

atgtcagcca ttgagagggt gtcagaggca atcgtcagca tccgaagaat ccagaccttt 60
ttgctacttg atgagatatc acagcgcaac cgtcagctgc cgtcagatgg taaaaagatg 120
gtgcatgtgc aggattttac tgctttttgg gataaggcat cagagacccc aactctacaa 180
ggcctttcct ttactgtcag acctggcgaa ttgttagctg tggtcggccc cgtgggagca 240
gggaagtcat cactgttaag tgccgtgtct ggggaattgg ccccaagtca cgggctggtc 300
agcgtgcatg gaagaattgc ctatgtgtct cagcagccct ggggtttctc gggaactctg 360
aggagtaata ttttatgttg gaagaaatac gaaaaggaaac gatatgaaaa agtcataaag 420
gcttgtgtct tgaaaaagga ttacagctg ttggaggatg gtgatctgac tgtgatagga 480
gatcggggaa ccacgtgag tggagggcag aaagcacggg taaaccttgc aagagcagtg 540
tatcaagatg ctgacatcta tctcctggac gatcctctca gtgcagtaga tgcggaagt 600
agcagacact tggtcgaact gtgtatttgt caaattttgc atgagaagat cacaatttta 660
gtgactcatc agttgcagta cctcaaagct gcaagtcaga ttctgatatt gaaagatggt 720
aaaatggtgc agaaggggac ttacactgag ttcttaaaat ctggtataga ttttggtccc 780
cttttaaaaga aggataatga ggaaagtgaa caacctccag ttccagggaac tcccacacta 840
aggaatcgta ccttctcaga gtcttcggtt tgggtctcaac aatcttctag accctccttg 900
aaagatggtg ctctggagag ccaagataca gagaatgtcc cagttacact atcagaggag 960
aaccgttctg aaggaaaagt tggttttcag gcctataaga attacttcag agctggtgct 1020
cactggattg tcttcatttt ccttattctc gagcaccacc accaccacca ctga 1074

```

<210> 682

<211> 224

<212> PRT

<213> Homo sapiens

<400> 682

```

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
      5                                10                    15

```

```

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala

```

	20		25		30										
Ile	Ala	Gly	Gln	Ile	Lys	Leu	Pro	Thr	Val	His	Ile	Gly	Pro	Thr	Ala
		35					40					45			
Phe	Leu	Gly	Leu	Gly	Val	Val	Asp	Asn	Asn	Gly	Asn	Gly	Ala	Arg	Val
	50					55					60				
Gln	Arg	Val	Val	Gly	Ser	Ala	Pro	Ala	Ala	Ser	Leu	Gly	Ile	Ser	Thr
	65				70					75					80
Gly	Asp	Val	Ile	Thr	Ala	Val	Asp	Gly	Ala	Pro	Ile	Asn	Ser	Ala	Thr
				85					90					95	
Ala	Met	Ala	Asp	Ala	Leu	Asn	Gly	His	His	Pro	Gly	Asp	Val	Ile	Ser
			100					105					110		
Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr
		115					120					125			
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	Met	Ile	Arg	Glu	Lys	Phe	Ala
	130					135					140				
His	Cys	Thr	Val	Leu	Thr	Ile	Ala	His	Arg	Leu	Asn	Thr	Ile	Ile	Asp
145					150					155					160
Ser	Asp	Lys	Ile	Met	Val	Leu	Asp	Ser	Gly	Arg	Leu	Lys	Glu	Tyr	Asp
				165					170					175	
Glu	Pro	Tyr	Val	Leu	Leu	Gln	Asn	Lys	Glu	Ser	Leu	Phe	Tyr	Lys	Met
			180					185					190		
Val	Gln	Gln	Leu	Gly	Lys	Ala	Glu	Ala	Ala	Ala	Leu	Thr	Glu	Thr	Ala
	195						200					205			
Lys	Gln	Arg	Trp	Gly	Phe	Thr	Met	Leu	Ala	Arg	Leu	Val	Ser	Asn	Ser
	210					215					220				

<210> 683

<211> 357

<212> PRT

<213> Homo sapiens

<400> 683

Met	Ser	Ala	Ile	Glu	Arg	Val	Ser	Glu	Ala	Ile	Val	Ser	Ile	Arg	Arg
				5				10						15	

Ile	Gln	Thr	Phe	Leu	Leu	Leu	Asp	Glu	Ile	Ser	Gln	Arg	Asn	Arg	Gln
		20						25					30		

Leu	Pro	Ser	Asp	Gly	Lys	Lys	Met	Val	His	Val	Gln	Asp	Phe	Thr	Ala
		35					40					45			

Phe	Trp	Asp	Lys	Ala	Ser	Glu	Thr	Pro	Thr	Leu	Gln	Gly	Leu	Ser	Phe
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

270

50	55	60
Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly Ala 65 70 75 80		
Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro Ser 85 90 95		
His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln 100 105 110		
Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys 115 120 125		
Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu 130 135 140		
Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly 145 150 155 160		
Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu 165 170 175		
Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp Pro 180 185 190		
Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu Cys 195 200 205		
Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His Gln 210 215 220		
Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp Gly 225 230 235 240		
Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly Ile 245 250 255		
Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln Pro 260 265 270		
Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu Ser 275 280 285		
Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly Ala 290 295 300		
Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu Glu 305 310 315 320		
Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe 325 330 335		
Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Glu His 340 345 350		
His His His His His 355		

<210> 684
<211> 96
<212> PRT
<213> Homo sapiens

<400> 684
Met Gly Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala
5 10 15
His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp
20 25 30
Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn
35 40 45
Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu
50 55 60
Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg Trp Gly Phe Thr Met
65 70 75 80
Leu Ala Arg Leu Val Ser Asn Ser Leu Glu His His His His His His
85 90 95

<210> 685
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 685
cgcccatggg gatccgggag aaatttgccc actgc

35

<210> 686
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 686
cgcctcgagg gagtttgaga ccagcctggc caaca

35

<210> 687
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 687
gcatggacca tatgtcagcc attgagaggg tgtcagag

38

<210> 688
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 688
ccgctcgaga ataaggaaaa tgaagacaat ccag

34

<210> 689
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 689
gttgaattca tgcacgggcc ccagggtg

27

<210> 690
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 690
cccctcgagt cactatggtc tgcctcttga

30

<210> 691
<211> 915
<212> DNA
<213> Homo sapiens

<400> 691
atgcatacc atcaccatca cacggccgag tccgataact tccagctgtc ccagggtggg 60
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120
accgttcata tggggcctac cgccttctct ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgacagag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatacatc cggtgacgtc atctcgggtg cctggcaaac caagtcgggc 360
ggcacgcgta cagggaaacgt gacattggcc gagggacccc cggccgaatt catgcacggg 420
ccccagggtg tggcacgctg ctccgagtgt gcttgtcctg ccttggctgc cacctctgcg 480
gggggtgcgtc tggagggggt ggaccggcca ccaaccttac ccagtcaagg aagtggatgg 540
ccatgttccc acagcctgag tggctgccac ctgatggctg atggagcaaa ggccttagga 600
aaagcagatg gcccttggcc ctaccttttt gttagaagaa ctgatgttcc atgtcctgca 660
gcgagtgagg ttggtggctg tgcccccagc tcttggcgcg ccctcgcaga ggtgactggt 720

<213> Homo sapiens

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
100 105 110

Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr
		115					120					125			

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met His Gly Pro Gln Val Leu
130 135 140

Ala Arg Cys Ser Glu Cys Ala Cys Pro Ala Leu Ala Ala Thr Ser Ala
145 150 155 160

Gly Val Arg Leu Glu Gly Val Asp Arg Pro Pro Thr Leu Pro Ser Gln
165 170 175

Gly Ser Gly Trp Pro Cys Ser His Ser Leu Ser Gly Cys His Leu Met
180 185 190

Ala Asp Gly Ala Lys Ala Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr
195 200 205

Leu Phe Val Arg Arg Thr Asp Val Pro Cys Pro Ala Ala Ser Glu Val
210 215 220

Gly Gly Cys Ala Pro Ser Ser Trp Arg Ala Leu Ala Glu Val Thr Gly
225 230 235 240

Cys Ser Leu Gly Pro Leu Gly Leu Ala Gln His Ala Gln Ala Ser Val
245 250 255

274

Leu Leu Leu Cys Tyr Lys Trp Ser His Ile Gly Glu Thr Ser Ser His
 260 265 270

Leu Arg Ser Lys Val Tyr Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu
 275 280 285

Lys Gly Leu Met Ser Leu Trp Ala Ser Trp Leu Ser Arg Gly Arg Pro
 290 295 300

<210> 693

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 693

cgaagtcacg tggaggccag cctc

24

<210> 694

<211> 29

<212> DNA

<213> Artificial Sequence

<220>

<223> PCR primer

<400> 694

cctgaccgaa ttcattaact ggcctggac

29

<210> 695

<211> 166

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(166)

<223> Xaa = Any Amino Acid

<400> 695

Met Gly His His His His His Val Glu Ala Ser Leu Ser Val Arg
 1 5 10 15
 His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile
 20 25 30
 Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser
 35 40 45
 Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly
 50 55 60
 Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys Val
 65 70 75 80
 Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp Pro

<211> 241
 <212> PRT
 <213> Homo sapiens

<400> 699

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Met Gln His His His His His His Leu Arg Val Pro Glu Pro Arg Pro
 1      5      10      15
Gly Glu Ala Lys Ala Glu Gly Ala Ala Pro Pro Thr Pro Ser Lys Pro
 20      25      30
Leu Thr Ser Phe Leu Ile Gln Asp Ile Leu Arg Asp Gly Ala Gln Arg
 35      40      45
Gln Gly Gly Arg Thr Ser Ser Gln Arg Gln Arg Asp Pro Glu Pro Glu
 50      55      60
Pro Glu Pro Glu Pro Glu Gly Gly Arg Ser Arg Ala Gly Ala Gln Asn
 65      70      75      80
Asp Gln Leu Ser Thr Gly Pro Arg Ala Ala Pro Glu Glu Ala Glu Thr
 85      90      95
Leu Ala Glu Thr Glu Pro Glu Arg His Leu Gly Ser Tyr Leu Leu Asp
 100     105     110
Ser Glu Asn Thr Ser Gly Ala Leu Pro Arg Leu Pro Gln Thr Pro Lys
 115     120     125
Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln Val Ile
 130     135     140
Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala Pro Glu
 145     150     155     160
Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln Val Lys
 165     170     175
Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln Leu Ser
 180     185     190
Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala Leu Lys
 195     200     205
Glu Glu Ala Phe Ser Arg Ala Ser Leu Val Ser Val Tyr Asn Ser Tyr
 210     215     220
Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro Ala Phe
 225     230     235     240
Trp

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<210> 700
 <211> 729
 <212> DNA
 <213> Homo sapiens

<400> 700

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atgcagcatc accaccatca ccacctcagg gttccggagc cgcggcccg gggaggcgaaa      60
gcggaggggg ccgcgccgcc gaccccgctc aagccgctca cgtccttct catccaggac      120
atcctgcggg acggcgcgca gcggcaaggc ggccgcacga gcagccagag acagcgcgac      180
ccggagccgg agccagagcc agagccagag ggaggacgca gccgcgccgg ggcgcagAAC      240
gaccagctga gcaccgggcc ccgcgcccg ccgatgagg ccgagacgct ggcagagacc      300
gagccagaaa ggcacttggg gtcttatctg ttggactctg aaaacacttc aggcgccctt      360
ccaaggcttc cccaaacccc taagcagccg cagaagcgct cccgagctgc cttctccac      420
actcaggtga tcgagttgga gaggaagttc agccatcaga agtacctgtc ggcccctgaa      480
cgggcccacc tggccaagaa cctcaagctc acggagaccc aagtgaagat atggttccag      540
aacagacgct ataagactaa gcgaaagcag ctctcctcgg agctgggaga cttggagaag      600
cactcctttt tgccggccct gaaagaggag gccttctccc gggcctccct ggtctccgtg      660
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277

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 <211> 27
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 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 701
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27

<210> 702
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 <212> DNA
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<220>
 <223> PCR primer

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33

<210> 703
 <211> 161
 <212> PRT
 <213> Homo sapiens

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 20 25 30
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 35 40 45
 Ala Val Asp Gly Ala Gly Gln Lys Lys Asp Arg Ala Trp Leu Arg Cys
 50 55 60
 Pro Glu Ala Val Ala Gly Phe Pro Leu Gly Ser Asp Cys Arg Glu Gly
 65 70 75 80
 Gly Arg Gln Gly Cys Gly Gly Ser Asp Asp Glu Asp Asp Leu Gly Val
 85 90 95
 Ala Pro Gly Leu Ala Pro Ala Trp Ala Leu Thr Gln Pro Pro Ser Gln
 100 105 110
 Ser Pro Gly Pro Gln Ser Leu Pro Ser Thr Pro Ser Ser Ile Trp Pro
 115 120 125
 Gln Trp Val Ile Leu Ile Thr Glu Leu Thr Ile Pro Ser Pro Ala His
 130 135 140
 Gly Pro Pro Trp Leu Pro Asn Ala Leu Glu Arg Gly His Leu Val Arg
 145 150 155 160
 Glu

<210> 704
 <211> 489
 <212> DNA
 <213> Homo sapiens

<400> 704
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 tgcttttccct ctgaggagtc aggagctgtg gatggtgctg gacagaagaa ggacagggcc 180
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 tccactccat cctccatctg gcctcagtg gtcattctga tcaactgaact gaccataccc 420
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 gagtagtga 489

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 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 705
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 Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
 35 40 45
 Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
 50 55 60
 Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
 65 70 75 80
 Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
 85 90 95
 Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
 100 105 110
 Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
 115 120 125
 Gly Pro Pro Ala
 130

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 <211> 31
 <212> DNA
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<220>
 <223> PCR primer

<400> 706
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31

<210> 707
 <211> 40
 <212> DNA
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<220>
 <223> PCR primer

<400> 707

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<210> 708

<211> 1203

<212> DNA

<213> Homo sapiens

<400> 708

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<211> 400

<212> PRT

<213> Homo sapiens

<400> 709

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Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
      35              40              45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
      50              55              60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
      65              70              75              80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
      85              90              95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser

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280

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115					120					125						
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	Ile	Thr	Tyr	Val	Pro	Pro	Leu	
130					135					140						
Leu	Leu	Glu	Val	Gly	Val	Glu	Glu	Lys	Phe	Met	Thr	Met	Val	Leu	Gly	
145					150					155					160	
Ile	Gly	Pro	Val	Leu	Gly	Leu	Val	Cys	Val	Pro	Leu	Leu	Gly	Ser	Ala	
165					170					175						
Ser	Asp	His	Trp	Arg	Gly	Arg	Tyr	Gly	Arg	Arg	Arg	Pro	Phe	Ile	Trp	
180					185					190						
Ala	Leu	Ser	Leu	Gly	Ile	Leu	Leu	Ser	Leu	Phe	Leu	Ile	Pro	Arg	Ala	
195					200					205						
Gly	Trp	Leu	Ala	Gly	Leu	Leu	Cys	Pro	Asp	Pro	Arg	Pro	Leu	Glu	Leu	
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225					230					235					240	
Cys	Phe	Thr	Pro	Leu	Glu	Ala	Leu	Leu	Ser	Asp	Leu	Phe	Arg	Asp	Pro	
245					250					255						
Asp	His	Cys	Arg	Gln	Ala	Tyr	Ser	Val	Tyr	Ala	Phe	Met	Ile	Ser	Leu	
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Leu	Thr	Leu	Ile	Phe	Leu	Thr	Cys	Val	Ala	Ala	Thr	Leu	Leu	Val	Ala	
305					310					315					320	
Glu	Glu	Ala	Ala	Leu	Gly	Pro	Thr	Glu	Pro	Ala	Glu	Gly	Leu	Ser	Ala	
325					330					335						
Pro	Ser	Leu	Ser	Pro	His	Cys	Cys	Pro	Cys	Arg	Ala	Arg	Leu	Ala	Phe	
340					345					350						
Arg	Asn	Leu	Gly	Ala	Leu	Leu	Pro	Arg	Leu	His	Gln	Leu	Cys	Cys	Arg	
355					360					365						
Met	Pro	Arg	Thr	Leu	Arg	Arg	Leu	Phe	Val	Ala	Glu	Leu	Cys	Ser	Trp	
370					375					380						
Met	Ala	Leu	Met	Thr	Phe	Thr	Leu	Phe	Tyr	Thr	Asp	Phe	Val	Gly	Glu	
385					390					395					400	

<210> 710
<211> 20
<212> PRT
<213> Homo sapiens

<400> 710
Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val
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Ser Val Arg Val
20

<210> 711
<211> 60
<212> DNA
<213> Homo sapiens

<400> 711
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<210> 712
<211> 10
<212> PRT
<213> Homo sapiens

<400> 712
Ala Ser Ala Cys Asp Val Ser Val Arg Val
5 10

<210> 713
<211> 30
<212> DNA
<213> Homo sapiens

<400> 713
gcctctgcct gtgatgtctc cgtacgtgtg

30

<210> 714
<211> 9
<212> PRT
<213> Homo sapiens

<400> 714
Ala Ser Ala Cys Asp Val Ser Val Arg
1 5

<210> 715
<211> 9
<212> PRT
<213> Homo sapiens

<400> 715
Ser Ala Cys Asp Val Ser Val Arg Val
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<210> 716
<211> 27

<212> DNA
<213> Homo sapiens

<400> 716
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27

<210> 717
<211> 19
<212> PRT
<213> Homo sapiens

<400> 717
Gly Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser
5 10 15

Ala Ser Asp

<210> 718
<211> 19
<212> PRT
<213> Homo sapiens

<400> 718
Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr
5 10 15

Met Val Leu

<210> 719
<211> 19
<212> PRT
<213> Homo sapiens

<400> 719
Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
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Gln Leu Leu

<210> 720
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<212> DNA
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<223> n = A,T,C or G

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<212> DNA
<213> Homo sapiens

<220>
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<210> 722
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<212> DNA
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<220>
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<223> n = A,T,C or G

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<211> 9
<212> PRT
<213> Homo sapiens

<400> 723
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1 5

<210> 724
<211> 9
<212> PRT
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<400> 724
Arg Met Pro Thr Val Leu Gln Cys Val
1 5

<210> 725
<211> 9
<212> PRT
<213> Homo sapiens

<400> 725
Asn Leu Cys Lys Phe Thr Glu Trp Ile
1 5

<210> 726
<211> 9
<212> PRT

<213> Homo sapiens

<400> 726

Met Leu Ile Lys Leu Asp Glu Ser Val

1 5

<210> 727

<211> 9

<212> PRT

<213> Homo sapiens

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Leu Leu Ala Asn Asp Leu Met Leu Ile

1 5

<210> 728

<211> 10

<212> PRT

<213> Homo sapiens

<400> 728

Leu Leu Ala Asn Gly Arg Met Pro Thr Val

1 5 10

<210> 729

<211> 10

<212> PRT

<213> Homo sapiens

<400> 729

Leu Met Leu Ile Lys Leu Asp Glu Ser Val

1 5 10

<210> 730

<211> 10

<212> PRT

<213> Homo sapiens

<400> 730

Val Leu Gln Cys Val Asn Val Ser Val Val

1 5 10

<210> 731

<211> 10

<212> PRT

<213> Homo sapiens

<400> 731

Gly Leu Leu Ala Asn Gly Arg Met Pro Thr

1 5 10

<210> 732

<211> 10

<212> PRT

<213> Homo sapiens

<400> 732

Thr Val Leu Gln Cys Val Asn Val Ser Val

285

1 5 10

<210> 733
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 733
 Gly Val Leu Val His Pro Gln Trp Val
 1 5

<210> 734
 <211> 9
 <212> PRT
 <213> Homo sapiens

<400> 734
 Val Leu Val His Pro Gln Trp Val Leu
 1 5

<210> 735
 <211> 1195
 <212> DNA
 <213> Homo sapiens

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 caacttccca tcaacaatat ttttataaaa ttccaatcct ggtcatcaac aaagtcttgc 420
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 <211> 339
 <212> PRT
 <213> Homo sapiens

<400> 736
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 20 25 30
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 35 40 45
 Thr Ala His Ala Asp Glu Phe Asp Cys Pro Ser Glu Leu Gln His Thr
 50 55 60
 Gln Glu Leu Phe Pro Gln Trp His Leu Pro Ile Lys Ile Ala Ala Ile
 65 70 75 80
 Ile Ala Ser Leu Thr Phe Leu Tyr Thr Leu Leu Arg Glu Val Ile His
 85 90 95
 Pro Leu Ala Thr Ser His Gln Gln Tyr Phe Tyr Lys Ile Pro Ile Leu
 100 105 110
 Val Ile Asn Lys Val Leu Pro Met Val Ser Ile Thr Leu Leu Ala Leu
 115 120 125
 Val Tyr Leu Pro Gly Val Ile Ala Ala Ile Val Gln Leu His Asn Gly
 130 135 140
 Thr Lys Tyr Lys Lys Phe Pro His Trp Leu Asp Lys Trp Met Leu Thr
 145 150 155 160
 Arg Lys Gln Phe Gly Leu Leu Ser Phe Phe Phe Ala Val Leu His Ala
 165 170 175
 Ile Tyr Ser Leu Ser Tyr Pro Met Arg Arg Ser Tyr Arg Tyr Lys Leu
 180 185 190
 Leu Asn Trp Ala Tyr Gln Gln Val Gln Gln Asn Lys Glu Asp Ala Trp
 195 200 205
 Ile Glu His Asp Val Trp Arg Met Glu Ile Tyr Val Ser Leu Gly Ile
 210 215 220
 Val Gly Leu Ala Ile Leu Ala Leu Leu Ala Val Thr Ser Ile Pro Ser
 225 230 235 240
 Val Ser Asp Ser Leu Thr Trp Arg Glu Phe His Tyr Ile Gln Ser Lys
 245 250 255
 Leu Gly Ile Val Ser Leu Leu Leu Gly Thr Ile His Ala Leu Ile Phe
 260 265 270
 Ala Trp Asn Lys Trp Ile Asp Ile Lys Gln Phe Val Trp Tyr Thr Pro
 275 280 285
 Pro Thr Phe Met Ile Ala Val Phe Leu Pro Ile Val Val Leu Ile Phe
 290 295 300
 Lys Ser Ile Leu Phe Leu Pro Cys Leu Arg Lys Lys Ile Leu Lys Ile
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325

330

335

Ser Gln Leu

<210> 737

<211> 2172

<212> DNA

<213> Homo sapiens

<400> 737

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ccatttttagt actatgggtg agtacatgga attgaagtct ggcttaaata ttcagaaagt 180
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<211> 2455

<212> DNA

<213> Homo sapiens

<400> 738

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gaaagatgtt	tctcaggttt	ttccttgacg	atcttcttct	tttctgattc	tgacaatgtt	300
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<211> 2455

<212> DNA

<213> Homo sapiens

<400> 739

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<210> 740

<211> 62

<212> PRT

<213> Homo sapiens

<400> 740

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Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn
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His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
          20                      25                      30

```

```

Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu
          35                      40                      45

```

```

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
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```

<210> 741

<211> 135

<212> PRT

<213> Homo sapiens

<400> 741

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Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
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290

Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg
20 25 30

Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu
35 40 45

Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu
50 55 60

Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala
65 70 75 80

Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly
85 90 95

Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro
100 105 110

Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile
115 120 125

Leu Leu Asn Tyr Gln Val Ser
130 135

<210> 742

<211> 77

<212> PRT

<213> Homo sapiens

<400> 742

Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln
5 10 15

Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His
20 25 30

Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro
35 40 45

Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln
50 55 60

Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu
65 70 75

<210> 743

<211> 60

<212> PRT

<213> Homo sapiens

<400> 743

Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly
5 10 15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
20 25 30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
 35 40 45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
 50 55 60

<210> 744

<211> 76

<212> PRT

<213> Homo sapiens

<400> 744

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
 5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
 20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
 35 40 45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
 50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
 65 70 75

<210> 745

<211> 76

<212> PRT

<213> Homo sapiens

<400> 745

Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp
 5 10 15

Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu
 20 25 30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly
 35 40 45

Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp
 50 55 60

Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys
 65 70 75

<210> 746

<211> 80

<212> PRT

<213> Homo sapiens

<400> 746

Met Leu Leu His Ser Ser Leu Val Asn Arg Ala Arg Leu Cys Leu Lys

292

5 10 15
 Asn Lys Gln Ile Asn Lys Gln Thr Asn Lys Thr Glu Arg Phe Cys Cys
 20 25 30
 Asn Val Gln Gly Ala Ile Cys Ser Phe Lys Lys Ile Ile Phe Gly Gln
 35 40 45
 Ala Gln Trp Leu Thr Pro Val Ile Pro Ala Leu Trp Glu Ala Lys Val
 50 55 60
 Gly Gly Ser Phe Glu Val Arg Ser Leu Arg Ser Ala Trp Pro Thr Trp
 65 70 75 80

<210> 747
 <211> 72
 <212> PRT
 <213> Homo sapiens

<400> 747
 Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro His Asn Pro
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 Ile Thr Ser His Gln Val Ser Ser Asp Thr Trp Asp Trp Val Gly Thr
 20 25 30
 Gln Ser Gln Thr Val Ser Asp Ala Ala Gly Ala Gly Asp Thr Glu Thr
 35 40 45
 Thr Gln Thr Trp Cys Leu Cys His Ser Ser Gly Leu Cys Leu Ser Pro
 50 55 60
 Gly Pro Pro Ser Pro Ser Met Val
 65 70

<210> 748
 <211> 77
 <212> PRT
 <213> Homo sapiens

<400> 748
 Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln
 5 10 15
 Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His
 20 25 30
 Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro
 35 40 45
 Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln
 50 55 60
 Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu
 65 70 75

<210> 749
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 749
 Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly
 5 10 15
 Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser
 20 25 30
 Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser
 35 40 45
 Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
 50 55 60

<210> 750
 <211> 76
 <212> PRT
 <213> Homo sapiens

<400> 750
 Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys
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 Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg
 20 25 30
 Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro
 35 40 45
 Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly
 50 55 60
 Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys
 65 70 75

<210> 751
 <211> 2479
 <212> DNA
 <213> Homo sapiens

<400> 751
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<210> 752

<211> 492

<212> PRT

<213> Homo sapiens

<400> 752

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Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
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```

```

Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
          20                      25                      30

```

```

Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
          35                      40                      45

```

```

Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
          50                      55                      60

```

```

Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
          65                      70                      75                      80

```

```

Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Ph Leu Val
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Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys

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Gly	Ala	Thr	Glu	Glu	Lys	Gly	Lys	Thr	Ser	Glu	Val	Leu	Asn	Ala	Ala
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Lys	Val	Leu	Leu	Ile	Glu	Thr	Gln	Arg	Cys	Asn	Ser	Arg	Tyr	Val	Tyr
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Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly
420 425 430

Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser
435 440 445

Asn Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly
450 455 460

Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe
465 470 475 480

Thr Asp Trp Ile Tyr Arg Gln Met Lys Ala Asn Gly
485 490

<210> 753

<211> 683

<212> DNA

<213> Homo sapiens

<400> 753

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gggcggcctg cagggacatg ggctataaga ataattttta ctctagccaa ggaatagtgg 660
atgacagcgg atccaccagc ttt 683
```

<210> 754

<211> 209

<212> PRT

<213> Homo sapiens

<400> 754

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Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
1 5 10 15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
20 25 30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35 40 45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50 55 60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65 70 75 80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85 90 95
```

297

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
 100 105 110
 Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
 115 120 125
 Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
 130 135 140
 Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met
 145 150 155 160
 Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
 165 170 175
 Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
 180 185 190
 Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
 195 200 205
 Phe

<210> 755
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 755
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr
 1 5 10 15
 Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg
 20 25

<210> 756
 <211> 35
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 756
 ggatccgccc ccaccatgtc actttctagc ctgct

35

<210> 757
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 757
 gtcgactcag ctggaccaca gccgcag

27

<210> 758
 <211> 34
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> PCR primer

<400> 758
ggatccgccc ccaccatggg ctgcaggctg ctct

34

<210> 759
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> PCR primer

<400> 759
gtcgactcag aaatcctttc tcttgac

27

<210> 760
<211> 936
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...()
<223> n = A,T,C or G

<400> 760
atgggctgca ggctgntctg ctgtgcggtt ctctgtctcc tgggagcggg ccccatggaa 60
acgggagtta cgcagacacc aagacacctg gtcattggaa tgacaaataa gaagtctttg 120
aaatgtgaac aacatctggg tcataacgct atgtattggg acaagcaaag tgctaagaag 180
ccactggagc tcatgtttgt ctacagtctt gaagaacggg ttgaaaacaa cagtgtgcca 240
agtcgcttct cacctgaatg ccccaacagc tctcacttat tccttcacct acacaccctg 300
cagccagaag actcggccct gtatctctgc gccagcagcc aagaccggac aagcagctcc 360
tacgagcagt acttcgggcc gggcaccagg ctccaggtca cagaggacct gaaaaacgtg 420
ttcccacccg aggtcgctgt gtttgagcca tcagaagcag agatctccca caccacaaaag 480
gccacactgg tgtgcctggc cacaggcttc taccctgacc acgtggagct gagctggtgg 540
gtgaatggga aggaggtgca cagtggggtc agcacagacc cgcagcccct caaggagcag 600
cccgcctca atgactccag atactgcctg agcagccgcc tgagggtctc ggccaccttc 660
tggcagaacc cccgcaacca cttccgctgt caagtccagt tctacgggct ctcgagaaat 720
gacgagtgga cccaggatag ggccaaacct gtcaccaga tcgtcagcgc cgaggcctgg 780
ggtagagcag actgtggctt cacctccgag tcttaccagc aaggggtcct gtctgccacc 840
atcctctatg agatcttgct aggaaggcc accttgtatg ccgtgctggt cagtgccctc 900
gtgctgatgg ccatgggtcaa gagaaaggat ttctga 936

<210> 761
<211> 834
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...()
<223> n = A,T,C or G

<400> 761
atgtcacttt ctacgctgct naaggtgggc acagcttcac tgtggctagg acctggcatt 60
gccagaaga taactcaaac ccaaccagga atgttcgtgc aggaaaagga ggctgtgact 120
ctggactgca catatgacac cagtgatcaa agttatggtc tcttctggta caagcagccc 180

```

agcagtgggg aaatgatttt ttttatttat caggggtctt atgacgagca aaatgcaaca 240
gaaggtcgct actcattgaa tttccagaag gcaagaaaaat ccgccaacct tgtcatctcc 300
gcttcacaac tgggggactc agcaatgtat ttctgtgcaa tgagagaggg cgcgggagga 360
ggaaacaaaac tcacctttgg gacaggcact cagctaaaaag tggaactcaa tatccagaac 420
cctgaccctg ccgtgtacca gctgagagac tctaaatcca gtgacaagtc tgtctgccta 480
ttcaccgatt ttgattctca aacaaatgtg tcacaaagta aggattctga tgtgtatatc 540
acagacaaaa ctgtgctaga catgaggtct atggacttca agagcaacag tgctgtggcc 600
tggagcaaca aatctgactt tgcattgtgca aacgccttca acaacagcat tattccagaa 660
gacaccttct tccccagccc agaaagttcc tgtgatgtca agctggtcga gaaaagcttt 720
gaaacagata cgaacctaaa ctttcaaaac ctgtcagtga ttgggttccg aatcctcttc 780
ctgaaagtgg ccgggtttta tctgctcatg acgtgcggc tggtgtccag ctga 834

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<210> 762

<211> 311

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> (1)...(311)

<223> Xaa = Any amino acid

<400> 762

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Met Gly Cys Arg Leu Xaa Cys Cys Ala Val Leu Cys Leu Leu Gly Ala
      5                      10                      15

```

```

Val Pro Met Glu Thr Gly Val Thr Gln Thr Pro Arg His Leu Val Met
      20                      25                      30

```

```

Gly Met Thr Asn Lys Lys Ser Leu Lys Cys Glu Gln His Leu Gly His
      35                      40                      45

```

```

Asn Ala Met Tyr Trp Tyr Lys Gln Ser Ala Lys Lys Pro Leu Glu Leu
      50                      55                      60

```

```

Met Phe Val Tyr Ser Leu Glu Glu Arg Val Glu Asn Asn Ser Val Pro
      65                      70                      75                      80

```

```

Ser Arg Phe Ser Pro Glu Cys Pro Asn Ser Ser His Leu Phe Leu His
      85                      90                      95

```

```

Leu His Thr Leu Gln Pro Glu Asp Ser Ala Leu Tyr Leu Cys Ala Ser
      100                      105                      110

```

```

Ser Gln Asp Arg Thr Ser Ser Ser Tyr Glu Gln Tyr Phe Gly Pro Gly
      115                      120                      125

```

```

Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Glu
      130                      135                      140

```

```

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
      145                      150                      155                      160

```

```

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu
      165                      170                      175

```

```

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
      180                      185                      190

```


300

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 763

<211> 277

<212> PRT

<213> Homo sapiens

<400> 763

Met Ser Leu Ser Ser Leu Leu Lys Val Val Thr Ala Ser Leu Trp Leu
5 10 15

Gly Pro Gly Ile Ala Gln Lys Ile Thr Gln Thr Gln Pro Gly Met Phe
20 25 30

Val Gln Glu Lys Glu Ala Val Thr Leu Asp Cys Thr Tyr Asp Thr Ser
35 40 45

Asp Gln Ser Tyr Gly Leu Phe Trp Tyr Lys Gln Pro Ser Ser Gly Glu
50 55 60

Met Ile Phe Leu Ile Tyr Gln Gly Ser Tyr Asp Glu Gln Asn Ala Thr
65 70 75 80

Glu Gly Arg Tyr Ser Leu Asn Phe Gln Lys Ala Arg Lys Ser Ala Asn
85 90 95

Leu Val Ile Ser Ala Ser Gln Leu Gly Asp Ser Ala Met Tyr Phe Cys
100 105 110

Ala Met Arg Glu Gly Ala Gly Gly Gly Asn Lys Leu Thr Phe Gly Thr
115 120 125

Gly Thr Gln Leu Lys Val Glu Leu Asn Ile Gln Asn Pro Asp Pro Ala
130 135 140

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu
145 150 155 160

Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser
165 170 175

Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp
180 185 190

Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala
195 200 205

Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe
210 215 220

Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe
225 230 235 240

Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe
245 250 255

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
260 265 270

Arg Leu Trp Ser Ser
275

<210> 764

<211> 1536

<212> DNA

<213> Homo sapiens

<400> 764

atgtacaacc	tggttgcgtgc	ctacgacaga	catgggggacc	acctgcagcc	cctggacctc	60
gtgcccgaatc	accagggtct	cacccctttc	aagctggctg	gagtggagg	taacactgtg	120
atgtttcagc	acctgatgca	gaagcgggaag	cacacccagt	ggacgtatgg	accactgacc	180
tcgactctct	atgacctcac	agagatcgac	tcctcagggg	atgagcagtc	cctgctggaa	240
cttatcatca	ccaccaagaa	gcgggaggct	cgccagatcc	tggaaccagac	gccggtgaag	300
gagctggtga	gcctcaagt	gaagcgggtac	gggcggccgt	acttctgcat	gctgggtgcc	360
atatatctgc	tgtacatcat	ctgcttcacc	atgtgctgca	tctaccgccc	cctcaagccc	420
aggaccaata	accgcacgag	cccccgggac	aacaccctct	tacagcagaa	gctacttcag	480
gaagcctaca	tgacccctaa	ggacgatata	cggctggctg	gggagctgg	gactgtcatt	540
ggggctatat	tcatacctgct	ggtagaggtt	ccagacatct	tcagaatggg	ggtcactcgc	600
ttctttggac	agaccatcct	tgggggccca	ttccatgtcc	tcatacatcac	ctatgccttc	660
atggtgctgg	tgaccatggg	gatgcggctc	atcagtgcca	gcggggagg	ggtacccatg	720
tcctttgcac	tcgtgctggg	ctggtgcaac	gtcatgtact	tcgcccagg	attccagatg	780
ctaggccct	tcacatcat	gattcagaag	atgatttttg	gcgacctgat	gcgattctgc	840
tggtgatgg	ctgtggtcat	cctgggcttt	gcttcagcct	tctatatcat	cttccagaca	900
gaggaccccg	aggagctagg	ccacttctac	gactacccca	tgccctgtt	cagcaccttc	960
gagctgttcc	ttacatcat	cgatggccca	gccaaactaca	acgtggacct	gcccttcatt	1020
tacagcatca	cctatgctgc	ctttgccatc	atcgccacac	tgctcatgct	caacctctc	1080
attgccatga	tgggcgacac	tactggcga	gtggcccatg	agcgggatga	gctgtggagg	1140
gccagattg	tggccaccac	ggtgatgctg	gagcggaagc	tgccctcgctg	cctgtggcct	1200
cgctccggga	tctgcggacg	ggagtatggc	ctgggagacc	gctggttcct	gcgggtggaa	1260
gacaggcaag	atctcaaccg	gcagcggatc	caacgctacg	cacaggcctt	ccacaccccg	1320
ggctctgagg	atttggaaca	agactcagtg	gaaaaactag	agctgggctg	tcccttcagc	1380

<213> Homo sapiens

atgtacaacc	tgttgctgtc	ctacgacaga	catggggacc	acctgcagcc	cctggacctc	60
gtgcccattc	accagggctc	cacccctttc	aagctggctg	gagtggagg	taacactgtg	120
atgtttcagc	acctgatgca	gaagcggaag	cacacccagt	ggacgtatgg	accactgacc	180
tgcactctct	atgacctcac	agagatcgac	tcctcagggg	atgagcagtc	cctgctggaa	240
cttatcatca	ccaccaagaa	gcgggagggt	cgccagatcc	tggaccagac	gccggtgaag	300
gagctgggtga	gcctcaagt	gaagcggtag	gggcggccgt	acttctgcat	gctgggtgcc	360
atatatctgc	tgtacatcat	ctgcttcacc	atgtgtctga	tctaccgccc	cctcaagccc	420
aggaccaata	accgcacgag	ccccgggac	aacacctct	tacagcagaa	gctactctcag	480
gaagcctaca	tgacccttaa	ggacgatata	cggctggctg	gggagctgg	gactgtcatt	540
ggggctatca	tcatcctgct	ggtagagggt	ccagacatct	tcagaatggg	ggtcactcgc	600
ttctttggac	agaccatcct	tgggggcccc	ttccatgtcc	tcatcatcac	ctatgccttc	660
atggtgctgg	tgaccatgg	gatgcggctc	atcagtcca	gcggggagg	ggtacccatg	720
tcctttgcac	tcgtgctggg	ctggtgcaac	gtcatgtact	tcgcccagg	attccagatg	780
ctaggcccct	tcaccatcat	gattcagaag	atgatttttg	gcgacctgat	gcgattctgc	840
tggctgatgg	ctgtggtcat	cctgggcttt	gcttcagcct	tctatatcat	cttcacagaa	900
gaggaccctg	aggagctagg	ccactctcac	gactaccccc	tggcctggt	cagcaccttc	960
gagctgttcc	ttaccatcat	cgatggcccc	gccaactaca	acgtggacct	gcccttcatg	1020
tacagcatca	cctatgctgc	ctttgccatc	atcgccacac	tgtcatgct	caacctcctc	1080
attgccatga	tgggcgacac	tactggcga	gtggcccatg	agcgggatga	gctgtggagg	1140
gccagattg	tggccaccac	ggtgatgctg	gagcgggaag	tgcctcgctg	cctgtggcct	1200
cgctccggga	tctgcggacg	ggagtatggc	ctgggagacc	gctggttcct	gcgggtggaa	1260
gacaggcaag	atctcaaccg	gcagcggatc	caacgctacg	cacaggcctt	ccacaccg	1320
ggctctgctg	atttggacaa	agactcagtg	gaaaaactag	agctgggctg	tcccttcagc	1380
ccccacctgt	cccttctcat	gccctcagtg	tctcgaagta	cctccgcga	cagtccaat	1440
tgggaaaggc	ttcggcaagg	gacctgagg	agagacctgc	gtgggataat	caacaggggt	1500
ctggaggacg	gggagagctg	ggaatatcag	atc			1533

<213> Homo sapiens

Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu
65 70 75 80

Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln
 85 90 95
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg
 100 105 110
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys
 115 120 125
 Phe Thr Met Cys Cys Ile Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn
 130 135 140
 Arg Thr Ser Pro Arg Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln
 145 150 155 160
 Glu Ala Tyr Met Thr Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu
 165 170 175
 Val Thr Val Ile Gly Ala Ile Ile Ile Leu Leu Val Glu Val Pro Asp
 180 185 190
 Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln Thr Ile Leu Gly
 195 200 205
 Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe Met Val Leu Val
 210 215 220
 Thr Met Val Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met
 225 230 235 240
 Ser Phe Ala Leu Val Leu Gly Trp Cys Asn Val Met Tyr Phe Ala Arg
 245 250 255
 Gly Phe Gln Met Leu Gly Pro Phe Thr Ile Met Ile Gln Lys Met Ile
 260 265 270

Phe Gly Asp Leu Met Arg Phe Cys Trp Leu Met Ala Val Val Ile Leu
 275 280 285
 Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe Gln Thr Glu Asp Pro Glu
 290 295 300
 Glu Leu Gly His Phe Tyr Asp Tyr Pro Met Ala Leu Phe Ser Thr Phe
 305 310 315 320
 Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro Ala Asn Tyr Asn Val Asp
 325 330 335
 Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala Ala Phe Ala Ile Ile Ala
 340 345 350
 Thr Leu Leu Met Leu Asn Leu Leu Ile Ala Met Met Gly Asp Thr His
 355 360 365
 Trp Arg Val Ala His Glu Arg Asp Glu Leu Trp Arg Ala Gln Ile Val
 370 375 380
 Ala Thr Thr Val Met Leu Glu Arg Lys Leu Pro Arg Cys Leu Trp Pro

385 390 395 400
 Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly Leu Gly Asp Arg Trp Phe
 405 410 415
 Leu Arg Val Glu Asp Arg Gln Asp Leu Asn Arg Gln Arg Ile Gln Arg
 420 425 430
 Tyr Ala Gln Ala Phe His Thr Arg Gly Ser Glu Asp Leu Asp Lys Asp
 435 440 445
 Ser Val Glu Lys Leu Glu Leu Gly Cys Pro Phe Ser Pro His Leu Ser
 450 455 460
 Leu Pro Met Pro Ser Val Ser Arg Ser Thr Ser Arg Ser Ser Ala Asn
 465 470 475 480
 Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg Arg Asp Leu Arg Gly Ile
 485 490 495
 Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser Trp Glu Tyr Gln Ile
 500 505 510

<210> 767

<211> 134

<212> PRT

<213> Homo sapiens

<400> 767

Met Tyr Asn Leu Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln
 5 10 15
 Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu
 20 25 30
 Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys
 35 40 45
 Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr
 50 55 60
 Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu
 65 70 75 80
 Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln
 85 90 95
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg
 100 105 110
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys
 115 120 125
 Phe Thr Met Cys Cys Ile
 130

305

<210> 768
 <211> 55
 <212> PRT
 <213> Homo sapiens

<400> 768
 Ala Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn Arg Thr Ser Pro Arg
 5 10 15
 Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln Glu Ala Tyr Met Thr
 20 25 30
 Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu Val Thr Val Ile Gly
 35 40 45
 Ala Ile Ile Ile Leu Leu Val
 50 55

<210> 769
 <211> 39
 <212> PRT
 <213> Homo sapiens

<400> 769
 Glu Val Pro Asp Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln
 5 10 15
 Thr Ile Leu Gly Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe
 20 25 30
 Met Val Leu Val Thr Met Val
 35

<210> 770
 <211> 19
 <212> PRT
 <213> Homo sapiens

<400> 770
 Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met Ser Phe Ala
 5 10 15
 Leu Val Leu

<210> 771
 <211> 52
 <212> PRT
 <213> Homo sapiens

<400> 771
 Gly Trp Cys Asn Val Met Tyr Phe Ala Arg Gly Phe Gln Met Leu Gly
 5 10 15
 Pro Phe Thr Ile Met Ile Gln Lys Met Ile Phe Gly Asp Leu Met Arg

BNSDOCID: <WO 0151633A2 | >

<210> 773
 <211> 1302
 <212> DNA
 <213> Homo sapiens

<400> 773

tggacaaagg	gggtcacaca	ttccttccat	acgggtgagc	ctctacctgc	ctgggtgctgg	60
tcacagttca	gcttcttcat	gatggtggat	cccaatggca	atgaatccag	tgtacatac	120
ttcatcctaa	taggcctccc	tggtttagaa	gaggctcagt	tctggttggc	cttcccattg	180
tgtccctct	accttattgc	tgtgctaggt	aacttgacaa	tcactctacat	tgtgoggact	240
gagcacagcc	tgcattgagcc	catgtatata	tttctttgca	tgctttcagg	battgacatc	300
ctcatctcca	cctcatccat	gcccataatg	ctggccatct	tctggttcaa	ttccactacc	360
atccagtgtg	atgcttgtct	gctacagatg	tttgccatcc	actccttata	tggcatggaa	420
tccacagtgc	tgtggcccat	ggcttttgac	cgctatgtgg	ccatctgtca	cccactgcgc	480
catgccacag	tacttacgtt	gcctcgtgtc	accataattg	gtgtggctgc	tgtggtgcgg	540
ggggctgcac	tgatggcacc	ccttcctgtc	ttcatcaagc	agctgccctt	ctgccgctcc	600
aatatccttt	cccattccta	ctgcctacac	caagatgtca	tgaagctggc	ctgtgatgat	660
atccgggtca	atgtcgtcta	tggccttata	gtcatcatct	ccgccattgg	cctggactca	720
cttctcatct	ccttctcata	tctgcttatt	cttaagactg	tgttgggctt	gacacgtgaa	780
gccagggcca	aggcatttgg	cacttgcgct	tctcatgtgt	gtgctgtgtt	catattctat	840
gtacctttca	tggattgtc	catggtgcat	cgcttttagca	agcggcgtga	ctctccgctg	900
cccgctcatct	tggccaatat	ctatctgctg	gttctcctg	tgtctaaacc	aattgtctat	960
ggagtgaaga	caaaggagat	tcgacagcgc	atccttcgac	ttttccatgt	ggccacacac	1020
gcttcagagc	cctaggtgtc	agtgatcaaa	cttcttttcc	attcagagtc	ctctgattca	1080
gatttttaatg	ttaacatttt	ggaagacagt	attcagaaaa	aaaatttcc	taataaaaaat	1140
acaactcaga	tccttcaaat	atgaaactgg	ttgggggaatc	tccatttttt	caatattatt	1200
ttcttctttg	ttttcttgc	acatataatt	attaataccc	tgactaggtt	gtggtttgag	1260
ggttattact	tttcatttta	ccatgcagtc	caaactctaaa	ct		1302

<210> 774
 <211> 2061
 <212> DNA
 <213> Homo sapiens

<400> 774

acgattcgac	agcgcaccc	tcgacttttc	catgtggcca	cacacgcttc	agagccctag	60
gtgtcagtga	tcaaacttct	tttccattca	gagtcctctg	attcagattt	taatgttaac	120
attttgggaag	acagtattca	gaaaaaaaat	ttccttaata	aaaatacaac	tcagatcctt	180
caaataatgaa	actggttggg	gaatctccat	tttttcaata	ttattttctt	ctttgttttc	240
ttgctacata	taattattaa	taccctgact	agggtgtggt	tggagggtta	ttacttttca	300
ttttaccatg	cagtccaaat	ctaaactgct	tctactgatg	gtttacagca	ttctgagata	360
agaatggtac	atctagagaa	catttgccaa	aggcctaagc	acggcaaagg	aaaataaaca	420
cagaatataa	taaaatgaga	taatctagct	taaaactata	acttccctct	cagaactccc	480
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Asp Asp Ile Arg Val Asn Val Val Tyr Gly Leu Ile Val Ile Ile Ser
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Gly Thr Cys Val Ser His Val Cys Ala Val Phe Ile Phe Tyr Val Pro
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310

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<212> PRT

<213> Homo sapiens

<400> 778

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314

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<213> Homo sapiens

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 Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
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<213> Homo sapiens

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Leu Glu Lys Arg Glu Ala Glu Ala Met Val Leu Gly Ile Gly Pro Val
 85 90 95
 Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp
 100 105 110
 Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu
 115 120 125
 Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala
 130 135 140
 Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile
 145 150 155 160
 Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro
 165 170 175
 Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg
 180 185 190
 Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu
 195 200 205
 Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro
 210 215 220
 Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile
 225 230 235 240
 Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala
 245 250 255
 Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser
 260 265 270
 Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly
 275 280 285
 Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr
 290 295 300
 Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met
 305 310 315 320
 Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln
 325 330 335
 Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp
 340 345 350
 Glu Gly Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile
 355 360 365
 Ser Leu Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly
 370 375 380
 Thr Arg Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala
 385 390 395 400
 Gly Ala Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala
 405 410 415
 Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr
 420 425 430
 Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr
 435 440 445
 Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser
 450 455 460
 Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val
 465 470 475 480
 Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Ala Leu Cys Gly
 485 490 495
 Ala Ser Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr
 500 505 510
 Glu Ala Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile
 515 520 525
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met
 530 535 540

Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser
545 550 555 560
Ala Ala Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val
565 570 575
Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala Gly Gly His His His
580 585 590
His His His
595

